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Can Promoting Awareness of Fetal movements and Focussing Interventions Reduce Fetal Mortality? - A stepped wedge cluster randomised trial (AFFIRM)

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For peer review only

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3 **1 Study Protocol**
4

5 2 Can Promoting Awareness of Fetal movements and Focussing Interventions Reduce
6 3 Fetal Mortality? - A stepped wedge cluster randomised trial (AFFIRM)
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3 40 **Abstract**
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5 41 *Background* - In 2013, the stillbirth rate in the UK was 4.2 per 1,000 live births,
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7 42 ranking 24th out of 49 high-income countries, with an annual rate of reduction of only
8
9 43 1.4% per year. The majority of stillbirths occur in normally formed infants, with
10
11 44 (retrospective) evidence of placental insufficiency the commonest clinical finding.
12
13 45 Maternal perception of reduced fetal movements (RFM) is associated with placental
14
15 46 insufficiency and increased risk of subsequent stillbirth.

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18 47 This study will test the hypothesis that the introduction of a package of care to
19
20 48 increase women's awareness of the need for prompt reporting of RFM and
21
22 49 standardised management to identify fetal compromise with timely delivery in
23
24 50 confirmed cases, will reduce the rate of stillbirth. Following the introduction of a
25
26 51 similar intervention in Norway the odds of stillbirth fell by 30%, but the efficacy of this
27
28 52 intervention (and possible adverse effects and implications for service delivery) have
29
30 53 not been tested in a randomised trial.

31
32
33 54 *Methods* - We describe a stepped wedge cluster trial design, in which participating
34
35 55 hospitals in the UK and Ireland will be randomized to the timing of introduction of the
36
37 56 care package. Outcomes (including the primary outcome of stillbirth) will be derived
38
39 57 from detailed routinely collected maternity data, allowing us to robustly test our
40
41 58 hypothesis. The degree of implementation of the intervention will be assessed in
42
43 59 each site. A nested qualitative study will examine the acceptability of the intervention
44
45 60 to patients and health care providers and identify process issues including barriers to
46
47 61 implementation.

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49
50 62 *Discussion* - The data provided by this study will inform the management of women
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52 63 with RFM; which has been recurrently identified as suboptimal in cases of stillbirth.
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54 64 This will provide robust evidence to determine whether increased maternal
55
56 65 awareness of RFM combined with a standardised management protocol to identify
57
58 66 acute or chronic fetal compromise can reduce stillbirth.

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3 67 *Trial Registration*

4
5 68 www.clinicaltrials.gov NCT01777022

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7
8 69 *Version*

9
10 70 Protocol Version 4.1, 18th October 2016

11
12 71 *Keywords*

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15 72 Reduced Fetal Movements; Perinatal Mortality; Stillbirth; Neonatal Death; Fetal
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17 73 Growth Restriction.

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22 75 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

23
24 76 • This trial directly addresses the need for studies of the information given to
25
26 77 women regarding fetal movements and the subsequent management of reduced
27
28 78 fetal movements identified by Confidential Enquiries into Antepartum Stillbirths,
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30 79 Systematic Reviews and the Stillbirth Priority Setting Partnership.

31
32 80 • A stepped-wedge cluster trial design in combination with routinely collected
33
34 81 maternity data allows the trial to be adequately powered to detect a difference in
35
36 82 stillbirth as a primary outcome.

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38 83 • The pragmatic nature of the study represents the potential impact of the
39
40 84 introduction of such standardised care into clinical practice.

41
42 85 • The nested qualitative study will provide information regarding the acceptability
43
44 86 of the intervention and identify barriers and facilitators to its adoption.

45
46 87 • The lack of information on resource use before and throughout the study period
47
48 88 limits the ability to understand the consequences of the intervention on maternity
49
50 89 unit workload.

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3 92 **INTRODUCTION**
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5 93 *Stillbirth*
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8 94 Stillbirth, defined in the UK as a baby with no signs of life after 24 weeks of completed
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10 95 pregnancy ¹, remains the major cause of perinatal mortality in high-income
11
12 96 environments, with a recent series of papers in the Lancet on stillbirth issue calling for
13
14 97 renewed action in this area ². There is no single “cause” of stillbirth, and a significant
15
16 98 proportion of stillbirths remain unexplained, but fetal growth restriction, maternal
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18 99 hypertension and low socioeconomic status are amongst the identifiable risk factors ³.
19
20 100 The concept that more can be done to reduce stillbirth in the UK and Ireland is
21
22 101 supported by data showing a marked variation in rates between resource rich
23
24 102 countries, when similar definitions of stillbirth are used ². Notably, the UK has a higher
25
26 103 rate than comparable resource rich countries such as Germany, Netherlands, New
27
28 104 Zealand and Norway with rates in the UK some 50% greater than those of the
29
30 105 Netherlands. Disappointingly, the annual rate of reduction in stillbirth from 2000 to
31
32 106 2014 in the UK was only 1.4% compared to 6.8% in the Netherlands and 2.8% in New
33
34 107 Zealand ². Rates of stillbirth in Scotland (3.7 per 1,000 births in 2014) and Ireland, at
35
36 108 (4.4 per 1,000 livebirths in 2013) are similar to rates in England and Wales at 4.2 per
37
38 109 1,000 livebirths (England and Wales, 2014) ⁴. The reduction of avoidable harm for
39
40 110 women and babies is viewed as a major priority for Government and its agencies
41
42 111 throughout the UK and Ireland. Consequently, several initiatives have been
43
44 112 developed by national governments in the UK and Ireland including the Scottish
45
46 113 Government Stillbirth Working Group, NHS England Saving Babies’ Lives Care
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48 114 Bundle and the Welsh Assembly 1000 Lives Plus strategy. These strategies have
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50 115 identified the need for better evidence to guide efforts to prevent stillbirths.
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52
53 116 Using a robust priority setting strategy ⁵ the Lancet Stillbirth’s series steering
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55 117 committee identified issues around detection and management of reduced fetal
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57 118 movements (RFM) amongst the top ten key research questions on prevention and
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3 119 management of stillbirth⁶. This was confirmed in the UK-based Stillbirth Priority
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5 120 Setting partnership involving over 1,700 parents and professionals which identified
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7 121 two relevant issues among the highest ranked research questions regarding stillbirth:
8
9 122 i) which investigations identify a fetus at risk of stillbirth after a mother believes she
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11 123 has experienced reduced fetal movements? and ii) would more accessible evidence-
12
13 124 based information on signs and symptoms of stillbirth risk, designed to empower
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15 125 women to raise concerns with healthcare professionals, reduce the incidence of
16
17 126 stillbirth?⁷ Thus, RFM has been identified as a highly-relevant area of study by
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19 127 parents, professionals and researchers.
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21 128

22 23 129 *Reduced Fetal Movements, Stillbirth and Placental Insufficiency*

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25
26 130 There is a clear association between maternal perception of RFM and late stillbirth
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28 131 dating back over four decades⁸. In a recent series of 2,000 women, the adjusted OR
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30 132 (95% CI) of late stillbirth in women with RFM (compared with controls) was 2.37
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32 133 (1.29-4.35)⁹. One international study of 1,714 women who experienced a stillbirth
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34 134 found that 30% had noted significant RFM prior to the diagnosis of stillbirth¹⁰.
35
36 135 Although the mechanisms have not been fully delineated, it is likely that RFM and
37
38 136 stillbirth are linked by a common pathology, that of placental dysfunction¹¹. There is
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40 137 good evidence linking placental dysfunction and RFM. Women who have fewer fetal
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42 138 movements on ultrasound immediately prior to caesarean section are more likely to
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44 139 have umbilical cord gas measurements indicative of acidaemia, hypoxaemia, and
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46 140 hypercapnia, compared with controls¹². Women delivering within one week of an
47
48 141 episode of RFM show differences in placental structure and function which are
49
50 142 reminiscent of those seen in fetal growth restriction (FGR) and stillbirth¹³.
51
52 143 Additionally, the odds of fetal growth restriction (FGR, defined as being at less than
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54 144 the 10th centile for gestation adjusted birthweight) were greater in women with RFM
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56 145 compared with controls (adjusted OR 1.6, 95% CI 1.1–2.2¹⁴). Taken together these
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3 146 data are strong evidence that placental dysfunction is associated with RFM, and a
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5 147 causative pathway seems likely.

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7 148 The evidence linking placental dysfunction and stillbirth is even stronger; a systematic
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9 149 review of placental pathology in stillbirths described abnormalities in up to 65% of
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11 150 cases¹⁵. Amongst the 291 stillbirths in Scotland in 2010, 137 (47%) had evidence of
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13 151 placental dysfunction¹⁶. Given that the placenta was examined in only 80% of
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15 152 stillbirths, the true prevalence of placental dysfunction is likely to be higher. In
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17 153 addition, between 20%-40% of stillborn babies are reported to have FGR, as defined
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19 154 by a birthweight less than the 10th centile¹⁷. Additionally, the Lancet report notes that
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21 155 “placental pathologies accounted for one in four deaths across all gestational ages,
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23 156 and were contributory or causal in more than half of cases”⁶. Given that stillbirth is
24
25 157 strongly related to placental dysfunction, and RFM is a “biomarker” of placental
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27 158 dysfunction then better management of women presenting with RFM focussing on the
28
29 159 detection of placental dysfunction might reduce the risk of stillbirth.

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33 161 *Formal Fetal Movement Counting*

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35 162 Although prenatal detection of FGR is improved by fetal movement counting¹⁸, a
36
37 163 systematic review¹⁹, and a large and influential cluster randomised trial (which
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39 164 dominates the systematic review) showed that routine fetal movement counting using
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41 165 the count to ten charts had no effect on perinatal mortality²⁰. Thus, the National
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43 166 Institute for Health and Social Care Excellence (NICE) recommended that “Routine
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45 167 formal fetal movement counting should not be offered”²¹. Importantly, the large
46
47 168 cluster randomised trial tested a specific alarm limit for RFM, but did not recommend
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49 169 a specific management strategy for women who did present with RFM. There were
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51 170 two important observations from this study, firstly that in both groups the perinatal
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53 171 mortality rate was lower than contemporary or subsequent periods in the UK and
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55 172 secondly that more women in the fetal movement counting arm came in with a live
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57 173 baby who subsequently died compared with the control arm (19 vs 11), suggesting

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3 174 that one reason the strategy failed to reduce perinatal mortality was inadequate
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5 175 investigation and management of those presenting with RFM ²⁰.

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9 177 *Efficacy of a package of intervention for RFM*

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11 178 Supportive data for the package of interventions used in this study comes from a

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13 179 large observational “clinical quality improvement study” in Norway which found a

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15 180 significant fall in rates of stillbirth (from 3.0/1,000 to 2.0/1,000 [OR 0.67 95% CI 0.48–

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17 181 0.93]) after the introduction of an intervention package consisting of written

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19 182 information for women about awareness of RFM combined with consensus guidelines

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21 183 for health professionals about their management ²². Although this study was not

22
23 184 randomised, and therefore constitutes only level II-3 evidence, it has informed

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25 185 recommendations from the Royal College of Obstetricians and Gynaecologists

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27 186 (RCOG) and Perinatal Society of Australia and New Zealand (PSANZ) that “women

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29 187 should be advised to be aware of their baby’s individual pattern of movements and

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31 188 that if they are concerned about a reduction in or cessation of fetal movements

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33 189they should contact their maternity unit” ^{23 24}. Following initial publication of the

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35 190 Norwegian study, a re-analysis was required as discrepancies between stillbirth rates

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37 191 in the study and the Medical Birth Registry of Norway were identified. This reanalysis

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39 192 found the reduction in stillbirth rates was of borderline statistical significance (OR

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41 193 0.72, 95% CI 0.50-1.03). The authors concluded that further studies were needed to

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43 194 determine whether this approach was associated with a reduction in stillbirth ²⁵.

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45 195 Importantly, in the Norwegian study, there was no increase in the proportion of

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47 196 women who presented with RFM when rates were compared before and after the

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49 197 intervention ²². However, women with RFM presented significantly earlier to hospital

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51 198 than they had hitherto, potentially allowing time for intervention to reduce perinatal

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53 199 mortality. These data suggest that a package of interventions encouraging women

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55 200 with RFM to present early to hospital, combined with a structured approach to their

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57 201 management might reduce rates of stillbirth without contributing to a large increase in

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3 202 admissions antenatally.
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7 204 *Optimal strategy for determining RFM*

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9 205 There is no uniform threshold of fetal movements below which perinatal morbidity
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11 206 increases ²⁶, and no evidence that a specific threshold performs better than maternal
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13 207 perception of reduced fetal movements alone ⁸. Therefore, guidelines from the RCOG
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15 208 and PSANZ ^{23 24}, informed by the Norwegian study ²² suggest that it is maternal
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17 209 *perception* of decreased fetal movement which is important.
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20
21 211 *Optimal strategy for investigation and management of women presenting with RFM.*

22
23 212 A recent systematic review found there are no proven strategies for the investigation
24
25 213 and management of women presenting with RFM ²⁷. Cardiotocography (CTG) is
26
27 214 routinely used to ascertain fetal wellbeing, and it is the cornerstone of the RCOG
28
29 215 guideline ²⁴. However, data from Norway, suggests that ultrasound assessment of
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31 216 fetal size is often the most helpful investigation, performing well on both an absolute
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33 217 basis, and compared with other interventions ²⁸. In a series of over 3,000 women with
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35 218 RFM, ultrasound (including measurement of fetal biometry and liquor volume) was
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37 219 found to be useful in detecting abnormalities in 11.6% of scans. In 71% of women in
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39 220 whom an abnormality was found, ultrasound was the only technique that detected an
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41 221 abnormality. Additionally, 85% of abnormalities detected by ultrasound, were
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43 222 important in informing the clinical management of the woman ²⁸. These data are
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45 223 supported by a smaller UK study which found that abnormalities detected on CTG or
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47 224 ultrasound scan were most strongly associated with adverse outcome in women with
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49 225 RFM, with identification of abnormal estimated fetal growth centile on scan being the
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51 226 test most highly predictive of poor outcome ²⁹. Perhaps this is not surprising, given the
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53 227 strong association between RFM and placental dysfunction and the central
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55 228 importance of ultrasound in the identification and management of small for gestational
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57 229 age babies ³⁰. Given these data, it is concerning that a survey of clinicians in Scotland
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3 230 showed that fewer than 5% would routinely refer women with RFM for ultrasound
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5 231 examination (unpublished data from June 2012), and a survey of 223 UK midwives
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7 232 and obstetricians described that 17.9% of respondents would perform an ultrasound
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9 233 scan³¹. These views of clinicians may reflect the variable quality of local guidelines,
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11 234 which are frequently not based on national recommendations, even those for which
12
13 235 there is strong evidence³². The variation in information given to women and
14
15 236 subsequent management of RFM has been highlighted as sources of suboptimal care
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17 237 in two confidential enquiries into antepartum stillbirth^{33 34}. Therefore, we believe that
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19 238 current investigation of women presenting with RFM is inadequate, hence using the
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21 239 best available evidence, we have drafted what we consider to be a robust evaluation
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23 240 protocol for investigation of women with RFM.
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28 242 *Potential harms of a package of care around increased awareness and optimised*
29 243 *management of RFM*

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32 244 Any clinical intervention which aims to improve outcomes also has the ability to do
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34 245 harm. Thus, it is essential that the intervention proposed is rigorously evaluated using
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36 246 the gold standard technique of a randomised trial, rather than being introduced as a
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38 247 service development. When the study began, there was a small window of
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40 248 opportunity to do this, as the enthusiasm to improve current management of RFM is
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42 249 such that routine introduction of the package of care is unlikely to be delayed much
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44 250 further than the current scheduled end date of this study. Possible harms of a
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46 251 package of care consisting of a management plan for identification and delivery of the
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48 252 “at risk” fetus, together with strategies for increasing pregnant women’s awareness of
49
50 253 the need to report early include increased maternal anxiety and increased
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52 254 intervention (including hospital admission, induction of labour and Caesarean section)
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54 255 which itself is associated with pregnancy related complications. The available
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56 256 evidence is reassuring on some of these issues. Encouraging women to be aware of
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3 257 fetal movement does not increase maternal anxiety ³⁵, and it appears to have a
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5 258 neutral effect on maternal- infant attachment ³⁶. In the Norwegian service
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7 259 development study, the package of care increased rates of follow up of women, but
8
9 260 there was no increase in admissions overall, admissions for induction or admissions
10
11 261 for emergency caesarean section ²² – again, whilst reassuring these outcomes
12
13 262 require formal evaluation in a randomised and relevant setting to the UK and Republic
14
15 263 of Ireland. The final possible harm of the package is around increased resource use,
16
17 264 and the opportunity cost of focussing on RFM rather than other potential methods to
18
19 265 prevent stillbirth.
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23 24 267 **RATIONALE**

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26
27 268 The aim of this study is to test the hypothesis that a package of interventions
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29 269 consisting of strategies for increasing pregnant women’s awareness of the need to
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31 270 report early when they perceive a reduction in fetal movements, followed with a
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33 271 management plan for identification and delivery of the “at risk” fetus in such women,
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35 272 will reduce rates of stillbirth.
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39 40 274 **STUDY OBJECTIVES**

41 42 275 *Primary Objective*

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44
45 276 The primary objective is to answer the research question ‘Does the introduction of a
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47 277 protocol for detection and management of decreased fetal movements reduce rates
48
49 278 of stillbirth?’ The secondary objectives are to answer the following research
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51 279 questions:

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54 280 • What is the effect of the intervention on rates of caesarean section and induction
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56 281 of labour?
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3 282 • What is the effect of the intervention on rates of admission to the neonatal
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5 283 intensive care unit?
6
7 284 • What is the effect of the intervention on the proportion of women with FGR
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9 285 remaining undelivered by 40 weeks gestation?
10
11 286 • What is the acceptability of such a package of care to pregnant women and their
12
13 287 health care providers?
14
15 288 • What other process outcomes are influenced by the intervention, such as health
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17 289 care provider/patient interactions?
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22 291 **ENDPOINTS**

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24
25 292 *Primary Outcome*

26
27 293 The primary endpoint is stillbirth (antepartum and intrapartum). We will use the UK
28
29 294 definition of stillbirth which is “a baby delivered without signs of life after 23⁺⁶ weeks”
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31 295 ⁴. Where gestation is uncertain we will include all babies with a birth weight of 500g
32
33 296 or more.
34
35

36 297 *Secondary Endpoints*

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38 298 Other measures of perinatal mortality including:

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41 299 • Stillbirth at 28 weeks gestation and above (WHO definition of stillbirth)
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43 300 • Stillbirth at 22 weeks gestation and above (international stillbirth alliance
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45 301 definition)
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48 302 • Stillbirths amongst normally formed infants of 22 weeks gestation and above,
49
50 303 24 weeks gestation and above and 28 weeks gestation and above
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53 304 • Perinatal mortality (defined as stillbirth at 24 weeks gestation and above and
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55 305 deaths in the first seven days of life)
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58 306 • Rates of caesarean section
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3 307 • Rates of induction of labour
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5 308 • Rates of admission to the neonatal intensive care unit (and their reasons)
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8 309 • Rates of admission to the neonatal intensive care unit for more than 48 hours
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10 310 • Proportion of infants with fetal growth restriction (less than the 10th centile,
11
12 311 customised for gender) remaining undelivered at or after 40 weeks gestation
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14
15 312 • Birthweight centile (according to <https://www.gestation.net>)
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17
18 313 • Rates of spontaneous vaginal delivery
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20 314 We will also collect the following data to allow adjustment for these variables:
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22 315 maternal age, maternity unit of delivery, birthweight, gestation of delivery, parity,
23
24 316 gestation, sex, smoking (current and ever), maternal body mass index (BMI), number
25
26 317 of babies (one or more), ethnicity (to allow a customised birthweight centile to be
27
28 318 generated), method of delivery, deprivation category (where available) and other
29
30 319 neonatal variables including Apgar score and encephalopathy.
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321 **STUDY DESIGN**

322 This is a multicentre, stepped wedge cluster randomised trial of a package of care
323 consisting of a management plan for identification and delivery of the 'at risk' fetus,
324 together with strategies for increasing pregnant women's awareness of the need to
325 report RFM early. The study will take place in participating hospitals in the UK and
326 Ireland (a complete list is available [http://www.crh.ed.ac.uk/affirm/randomised-](http://www.crh.ed.ac.uk/affirm/randomised-hospitals/)
327 [hospitals/](http://www.crh.ed.ac.uk/affirm/randomised-hospitals/)). A nested qualitative study will examine the acceptability of the
328 intervention to patients and health care providers and identify process issues
329 (barriers to implementation). Clinical audit conducted after the change in practice will
330 be used to determine the effect of interventions on process outcomes (e.g. number of
331 women presenting with reduced fetal movements, interval between perceiving

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3 332 reduced fetal movements and presentation to hospital, number of ultrasound scans,
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5 333 number of admissions for induction of labour). A diagram indicating randomisation of
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7 334 hospital groupings in the stepped wedge design is shown in Figure 1.
8

9
10 335 The interventions will be introduced over a 33 month period. Data will be collected
11
12 336 over a 36 month period. Data in the 'active phase' after introduction of the
13
14 337 intervention will be compared to data in the 'control phase' – the period during which
15
16 338 usual care processes in study sites are followed from study start to the time of
17
18 339 introduction of the intervention. Given that it will take individual units some time (a) to
19
20 340 effect change in management in their unit from time of introduction of the intervention
21
22 341 and (b) that it will take some time for this change in practice to impact on clinical
23
24 342 outcomes, we plan a "washout" period of two months after the introduction of the
25
26 343 intervention during which data will not be included in either group for analysis.
27

28 344

31 345 **STUDY POPULATION**

33 346 *Number of participants*

34
35
36 347 Participants will be those delivering at all the sites over the study period (36 months).
37
38 348 All eligible women will be recruited to the cluster randomised controlled trial. Based
39
40 349 on previous delivery numbers, after accounting for a washout period of two months
41
42 350 (and assuming no withdrawals or losses to follow up) this is estimated to be a total of
43
44 351 around 143,140 women per annum. A subset of around 30 participating women and
45
46 352 30 midwives, sonographers and obstetricians will be recruited to the nested
47
48 353 qualitative study, which is based in the Scottish sites.

50 354 *Inclusion criteria*

51
52
53 355 We will include all women delivering at one of the participating maternity units for the
54
55 356 duration of the study. Women who have been seen at any of the maternity units but
56
57 357 who deliver at home will not be included. The duration of the study will be 42 months
58
59
60

1
2
3 358 from the start of the trial (01/02/2014). For practical reasons, participants for the
4
5 359 nested qualitative study will be recruited from the participating units in Scotland.

6
7 360 *Exclusion criteria*

8
9 361 We will exclude women as follows:

- 10
11
12 362 • Women for whom data on delivery outcomes is still unavailable four months after
13
14 363 the date of delivery
15
16
17 364 • Women delivering in the “washout” period in each unit.

18
19
20 365 Members of the trial management group and participants who do not
21
22 366 speak/understand English will be excluded from participating in the nested qualitative
23
24 367 study.

25
26 368 *Identifying participants*

27
28
29 369 Women will be identified from those whose data is included in routine data returns
30
31 370 from each unit. Potential participants for the nested qualitative study will be identified
32
33 371 from those attending antenatal clinics in participating hospitals, and/or local staff.

34
35 372 *Consenting participants*

36
37
38 373 The main study is a stepped wedge cluster randomised trial of a package of care
39
40 374 which would be introduced in many of the participating units regardless of whether
41
42 375 the trial was on-going or not and the trial uses only routinely collected data on
43
44 376 participants. The ethics committee indicated that formal individual patient consent is
45
46 377 not necessary for the main trial. Participants in the nested qualitative study will be
47
48 378 asked for individual consent.

49
50 379 *Screening for eligibility*

51
52
53 380 As participants are not directly recruited we will not perform any specific screening
54
55 381 tests for this aspect of this project. Participants for the nested qualitative study will
56
57 382 be: (i) Pregnant women attending hospitals who are participating in the main trial in
58
59
60

1
2
3 383 Scotland. Purposive sampling will ensure that the final sample set includes women
4
5 384 who have and who have not experienced RFM, both before and after the introduction
6
7 385 of the intervention; (ii) Hospital staff (including midwives, ultrasonographers and
8
9 386 obstetricians/radiologists) working in participating hospitals in Scotland. There will be
10
11 387 no specific screening tests for eligibility for the nested qualitative study, except that
12
13 388 women who have experienced a stillbirth in the index pregnancy will not be
14
15 389 approached.

16
17
18 390 *Ineligible and non-recruited participants*

19
20 391 Potential participants for the nested qualitative study who are not approached or who
21
22 392 decline will have no specific interventions / procedures.

23
24
25 393 *Withdrawal of Study Participants*

26
27 394 The nature of a cluster randomised study is such that it is not possible for the
28
29 395 participant to withdraw from the “cluster” unless she changes maternity unit part way
30
31 396 through her pregnancy. We plan to collect routinely recorded anonymised data;
32
33 397 patients have the right to opt out of having their data used – if this happens their data
34
35 398 would be excluded from the study database (e.g. under the Confidentiality and
36
37 399 Security advisory Group Report 2002 and the Data Protection Act (1998)
38
39 400 requirements for fair processing of data). Participants in the nested qualitative study
40
41 401 who wish to withdraw will be allowed to do so. Their data will be retained and used,
42
43 402 unless they additionally indicate that they wish to withdraw their data.

44
45
46 403 **RANDOMISATION**

47
48 404 *Randomisation Procedures*

49
50
51 405 This is a cluster-randomised, stepped-wedge design trial wherein maternity units
52
53 406 rather than individual patients are randomised. All units will implement the fetal
54
55 407 movement monitoring intervention at some point during the trial; the random element
56
57 408 is the time point at which this will occur, the so-called “step” of the stepped-wedge

1
2
3 409 design. Participating maternity units will be blinded to their randomly allocated time
4
5 410 point until the time this is required to be revealed to enable the necessary training in
6
7 411 the implementation of the intervention to be delivered. Primary and secondary
8
9 412 outcomes of the trial will be gathered in a blinded manner via routinely collected data
10
11 413 sources.

12
13 414 Groups of units which are in close proximity to each other will be treated as strata for
14
15 415 the purposes of randomisation. This will assist with the feasibility of delivering the
16
17 416 training for and implementation of the intervention. Furthermore, this local
18
19 417 synchronisation of the intervention implementation will minimise the chances of
20
21 418 contamination (introduction of the intervention prematurely) from maternity units
22
23 419 which have already implemented the intervention to those not yet randomised.

24
25
26 420 The order in which the strata of units step in to implement the intervention will be
27
28 421 determined by computer generated random numbers from a uniform distribution. The
29
30 422 randomisation list will be held by the Edinburgh Clinical Trials Unit (ECTU). The
31
32 423 identities of the research team staff whose roles in the trial require them to be
33
34 424 unblinded to randomisation codes will be recorded in the trial master file (TMF).

35 36 37 425 *Treatment Allocation*

38
39 426 Participating sites will be randomised to the intervention or conventional clinical
40
41 427 management. All units will be providing conventional treatment at baseline according
42
43 428 to local practice – this is the treatment established before the study starts. Sites will
44
45 429 be randomised to “active” treatment in turn as described above. Active treatment will
46
47 430 consist of a package of care consisting of a management plan for identification and
48
49 431 delivery of the ‘at risk’ fetus, together with strategies for increasing pregnant women’s
50
51 432 awareness of the need to report RFM early. The recommended management plan for
52
53 433 identification and delivery of the “at risk” fetus is shown in Figure 2. Practice change
54
55 434 in the active units will be achieved by: (i) written/email information to all clinicians
56
57 435 (doctors, midwives and ultrasonographers) in each unit about the study protocol and
58
59
60

1
2
3 436 amendment of the local protocol for Reduced Fetal Movements (RFM) to that of the
4
5 437 study protocol; (ii) a short web-based training package taking approximately one hour
6
7 438 to complete for all clinicians in each centre and (iii) training /information sessions to
8
9 439 run in each unit and (iv) posters in each unit to describe the practice change.
10
11 440 Strategies for encouraging clinicians to increase pregnant women's awareness of
12
13 441 fetal movement will include all the above and also a fetal movement leaflet for
14
15 442 pregnant women (shown in Supplementary Information 1). Once units have begun
16
17 443 active treatment it is not anticipated that they will return to conventional treatment.
18
19 444 We will conduct an audit of women presenting with reduced fetal movements and
20
21 445 assess the proportion of staff completing the online training to assess the extent to
22
23 446 which sites have followed the intervention plan.
24
25
26 447 Units will be informed about treatment allocation as near as possible to the
27
28 448 implementation of the "active" treatment. For practical purposes, we anticipate that
29
30 449 each unit will need around three months' notice before the "active" treatment is
31
32 450 introduced, hence units will be informed of the timing of their treatment allocation
33
34 451 (step) three months before the active treatment is due to start. The treatment
35
36 452 allocation will not be administered blind and there are no restrictions on concomitant
37
38 453 care or other interventions during the study, hence there is no need for emergency
39
40 454 unblinding and there are no stopping rules for the study.

42 **DATA COLLECTION**

43
44
45 456 For the main trial, data will be accessed from the information routinely collected
46
47 457 during the clinical management of the patient. For consistency, we will normally only
48
49 458 include data items which become available within four months after the delivery date
50
51 459 in question, although we may seek advice from the independently-chaired trial
52
53 460 steering committee (TSC) about exceptions as they arise. Different data sources will
54
55 461 be used for different regions of the study: (i) In Scotland the source data will be
56
57 462 SMR2 and the Scottish Birth record, (ii) In Ireland the source data will be the National
58
59
60

1
2
3 463 Perinatal Reporting System (NRPS http://www.esri.ie/health_information/nprs), (iii) In
4
5 464 Northern Ireland, the source data will be the Northern Ireland maternity Statistics
6
7 465 database (NIMATS), (iv) In England and Wales, the source data will be the ONS, or
8
9 466 other relevant body. Data will be collected retrospectively on an annual basis from all
10
11 467 sources. We will assume that data unavailable four months after the woman
12
13 468 delivered is likely to be unobtainable (but see note in Study Design section above).
14
15 469 Thus, data on the first year of the study will be collected at month 16; data on the
16
17 470 second year will be collected at month 28 etc.

18
19
20 471 Data are routinely collected. A formal request for data access will be made at the
21
22 472 start of the study. This will require (i) in Scotland – Privacy Advisory Committee
23
24 473 approval and a formal approach to NHS Scotland Information Services Division (ISD)
25
26 474 (ii) in Ireland a formal approach to NRPS (iii) NIMATS in Northern Ireland (iv) in
27
28 475 England and Wales a formal approach will be made to the relevant bodies.

29
30 476 Data will then be sent to the electronic Data Research and Innovation Service
31
32 477 (eDRIS) National Safe Haven (NHS National Services Scotland) by secure file
33
34 478 transfer protocol (or other similar) for storage and subsequent analysis within a
35
36 479 secure project area (dedicated to the AFFIRM study). Further information on the
37
38 480 National Safe Haven is available at [http://www.isdscotland.org/Products-and-](http://www.isdscotland.org/Products-and-Services/eDRIS/Becoming-an-eDRIS-User/#NSS-National-Safe-Haven)
39
40 481 [Services/eDRIS/Becoming-an-eDRIS-User/#NSS-National-Safe-Haven](http://www.isdscotland.org/Products-and-Services/eDRIS/Becoming-an-eDRIS-User/#NSS-National-Safe-Haven). Briefly, the
41
42 482 National Safe Haven is located on a secure server, in which trusted and authorised
43
44 483 researchers can analyse individual level data while maintaining the utmost
45
46 484 confidentiality. It is anticipated that all study analysis will be done within the Safe
47
48 485 Haven, using one of the available statistical packages (e.g. R, SPSS).

49
50
51 486 Identifiers on Scottish data within the National Safe Haven are concealed from
52
53 487 researchers. Data from outwith Scotland will be anonymised before submission to the
54
55 488 National Safe Haven. We propose that data submitted to the National Safe Haven
56
57 489 will be “anonymised” by the data provider. However, we propose that the
58
59
60

1
2
3 490 anonymisation link will be retained at the source so that it will be possible to re-link
4
5 491 data retrospectively. The rationale for retaining the ability of local data guardians to
6
7 492 re-link data is because it is important to retain the possibility of identifying individual
8
9 493 patients retrospectively. Examples include: (i) It is possible that some additional
10
11 494 important data may be available at a late stage on individual participants – e.g. in the
12
13 495 scenario where the woman or baby had a major adverse event and spent a long time
14
15 496 in hospital before discharge or death and (ii) Although our protocol and outcome
16
17 497 analysis does not require identifiable data, we believe this will be a ‘once in a lifetime’
18
19 498 study, and that subsequent secondary analyses could yield important information for
20
21 499 patients and for policy makers. If retrospective identification is not possible, this will
22
23 500 limit further analysis. One likely example of future analyses is to determine the effect
24
25 501 of the intervention on different causes of stillbirth. This is outwith the scope of the
26
27 502 current protocol, but could be done relatively straightforwardly, by linking nationally
28
29 503 recorded information on “cause” of stillbirth to our study database. We anticipate that
30
31 504 such additional analyses would require additional ethics approval, but without a
32
33 505 process by which to re-link data, it will not be possible to perform such subsequent
34
35 506 analyses.

37
38 507 All Investigators and study site staff involved with this study will comply with the
39
40 508 requirements of the Data Protection Act 1998 (or equivalent for those outwith the UK)
41
42 509 with regard to the collection, storage, processing and disclosure of personal
43
44 510 information and will uphold the Act’s core principles. Published results will not contain
45
46 511 any personal data that could allow identification of an individual participant.

48
49 512 In addition to the data recorded above, all sites will be asked to provide a copy of
50
51 513 their guidelines around (i) maternal awareness of RFM and (ii) management of
52
53 514 women presenting with RFM. Copies of guidelines will be sought by the study office
54
55 515 (a) at the start of the study (b) immediately before initiation of the intervention in each
56
57 516 specific unit and (c) six months after initiation of the intervention in each specific unit.

1
2
3 517 For the nested qualitative study, we will perform interviews of healthcare workers and
4
5 518 a small nested cohort of pregnant women about their experiences of fetal movement
6
7 519 and of this intervention. We shall ensure a diversity of age and include nulliparous
8
9 520 and multiparous women (n=30 in total). Ten interviews will be conducted with each of
10
11 521 the following groups of health care providers: obstetricians, midwives and
12
13 522 sonographers/radiologists. The interviews will take a semi-structured format
14
15 523 (sensitising and piloting interviews will be conducted prior to the commencement of
16
17 524 the trial and in the first month of the nested qualitative study). This format will ensure
18
19 525 the same categories of data will be obtained from each participant but also allow
20
21 526 individual responses to be fully explored.
22
23
24
25

527

528 **STATISTICS AND DATA ANALYSIS**

529 *Sample size calculation*

30
31 530 The sample size is the number of women delivering in hospitals participating in the
32
33 531 study. This was initially planned to include sites in Scotland, totalling around 58,000
34
35 532 deliveries per year with 16 consultant led maternity units, 20 smaller units each
36
37 533 delivering less than 350 babies per year, and seven units delivering less than five
38
39 534 births per year. The units involved in Perinatal Ireland (an all-Ireland research
40
41 535 consortium across 7 academic sites in Ireland currently funded by the Health
42
43 536 Research Board, Ireland) have 50,000 births per year with seven large sites.
44
45 537 Combining one or two of the smaller units and one larger unit into a single “hospital
46
47 538 group” for each local area could provide 24 hospital “groups” – the details of hospital
48
49 539 groupings will be reviewed and finalised immediately prior to randomisation. In total,
50
51 540 36 sites expressed interested in participating in the study, although 2 were unable to
52
53 541 participate in the study and withdrew before randomisation. In total, 34 units were
54
55 542 randomised, these were situated throughout the UK and Ireland (10 in England, 4 in
56
57 543 Ireland, 15 in Scotland and 5 in Wales) with 143,140 births per annum.
58
59
60

1
2
3 544 We calculated statistical power using the methodology for stepped wedge designs
4
5 545 proposed in Hussey and Hughes (2007)³⁷. First, we analysed stillbirth event data
6
7 546 from the Scottish Perinatal and Infant Mortality and Morbidity Report (SPIMMR)
8
9 547 covering years 2005-2010¹⁶ to determine estimates of between- and within-unit
10
11 548 variability in stillbirth rate. Analysis was by generalized linear mixed model for binary
12
13 549 outcomes. The power calculation, as per equations (#7) and (#8) in³⁷ assumed:
14
15 550 significance level 5%; analysis by generalized linear mixed model; deliveries equally
16
17 551 distributed across hospital groupings; baseline stillbirth rate 0.438%¹⁶; between-
18
19 552 cluster variance 0.00816.

20
21
22 553 Finally, the statistical power depends on the number of groups in which the
23
24 554 intervention is implemented at each stage of the stepped wedge design and the
25
26 555 duration of recruitment at each “step”. Our study design proposes sequential
27
28 556 introduction of the intervention into three hospital groups at a time at four month
29
30 557 intervals over a 32 month period. It is anticipated that unavailability of data and
31
32 558 women asking to withdraw their data will be less than 1%. This would give 89.9%
33
34 559 power to detect a 30% relative risk reduction under the intervention and 77.0% power
35
36 560 to detect a 25% reduction. A 30% risk reduction was seen in the Norwegian study;
37
38 561 the anticipated effect sizes of 25% and 30% relative reduction take into account that
39
40 562 the intervention will not have the power to reduce all stillbirths, since 20% of stillbirths
41
42 563 in Ireland³⁸ and 15% in Scotland¹⁶ are associated with congenital anomaly.

43 44 45 564 *Proposed analyses*

46
47 565 For the binary primary and secondary outcomes, data will be analysed by
48
49 566 generalized linear mixed model with a random effect for hospital and fixed effects for
50
51 567 the intervention implementation, study time period and calendar year. A site by
52
53 568 intervention interaction random effect will be included in the model and retained if it
54
55 569 explains an important proportion of the variability in outcomes. The primary analysis
56
57 570 of data will be on an intention to treat basis (the design of the trial means it is not
58
59
60

1
2
3 571 possible to determine individual patient /caregiver compliance with the intervention).
4
5 572 An “on treatment” variable will be calculated for which women will be grouped as
6
7 573 active or control according to when the intervention was actually implemented in their
8
9 574 site, instead of when the site was randomised to implement the intervention. The
10
11 575 primary outcome will be reanalysed using the “on treatment” classification in a
12
13 576 sensitivity analysis. There are no planned imputations for missing data. However, if
14
15 577 the missing data rate for smoking status during pregnancy is relatively high an
16
17 578 imputation technique will be devised. The imputation method will be informed using
18
19 579 smoking history at booking and age at delivery ³⁹. A pre-specified subgroup analysis
20
21 580 will be performed for babies with and without congenital anomalies, and will be
22
23 581 implemented by testing for an intervention by congenital anomaly interaction added
24
25 582 to the generalised linear mixed model described above. No formal interim analyses
26
27 583 for efficacy or safety will be performed. A full statistical analysis plan was finalised
28
29 584 and signed on 05/10/2016.

31 585 *Qualitative Data*

32
33
34 586 For the nested qualitative study, the data will be audio recorded and transcribed.
35
36 587 The data will be coded thematically and an analytical framework developed to make
37
38 588 sense of patient experience of fetal movement and the intervention and also health
39
40 589 care providers’ perspectives and experiences. NVivo will be utilised to support the
41
42 590 analysis.

43 44 45 591 *Process outcomes*

46
47
48 592 The process outcomes being assessed by the (rates of induction of labour, number
49
50 593 of women presenting with reduced fetal movements, interval between perceiving fetal
51
52 594 movements and presenting to hospital) will be analysed using the same methods as
53
54 595 for the main trial, with the exception of the continuous outcome (interval between
55
56 596 perceiving fetal movements and presenting to hospital) which will be analysed using
57
58 597 a normal linear mixed model.

1
2
3 598 **ADVERSE EVENTS**
4

5 599 This is not a Clinical Trial of an Investigational Medicinal Product (CTIMP) so adverse
6
7 600 events will not be formally reported. Stillbirth and other measures of fetal and
8
9 601 maternal morbidity are outcomes of the study. The purpose of the intervention is to
10
11 602 reduce such adverse events. Therefore, due to the low risks for this trial, a separate
12
13 603 DMC is not required and the Trial Steering Committee (TSC) will cover any
14
15 604 responsibilities normally allocated to a DMC. If considered necessary, the TSC may
16
17 605 review unblinded data for the study, including morbidity and mortality indices. No
18
19 606 other adverse event reporting will be undertaken.

20
21
22 607 **TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS**
23

24 608 The trial will be coordinated by a Project Management Group, consisting of the grant
25
26 609 holders and the Trial Manager. The Chief Investigator (JN) will lead the project
27
28 610 management group. The Trial Manager will oversee the study and will be
29
30 611 accountable to the Chief Investigator. A TSC will be established to oversee the
31
32 612 conduct and progress of the trial. The terms of reference and a draft template for
33
34 613 reporting will be ratified in one of the early meetings of the TSC.

35
36
37 614 Investigators and institutions involved in the study will permit trial related monitoring
38
39 615 and audits on behalf of the co-sponsors (ACCORD: Academic and Clinical Central
40
41 616 Office for Research & Development - Joint office for University of Edinburgh and
42
43 617 NHS Lothian, Sponsor contact: ray.french@ed.ac.uk), research ethics committee
44
45 618 (REC) review, and regulatory inspection(s). In the event of an audit or monitoring, the
46
47 619 Investigator agrees to allow the representatives of the sponsor direct access to all
48
49 620 study records and source documentation. In the event of regulatory inspection, the
50
51 621 Investigator agrees to allow inspectors direct access to all study records and source
52
53 622 documentation.
54

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56 623
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2
3 624 *Study monitoring and audit*
4

5 625 The sponsor determined that as no individual participants were recruited to the
6
7 626 intervention, and it was not a clinical trial of an investigational medicinal product
8
9 627 (CTIMP) no formal monitoring and audit was required.
10

11 628

12
13
14 629 *Good Clinical Practice and Ethical Conduct*
15

16
17 630 The study will be conducted in accordance with the principles of the research
18
19 631 governance framework operational and good clinical practice in the relevant country.
20

21 632 A favorable ethical opinion has been obtained from the Scotland A REC (Reference
22
23 633 13/SS/0001) and local research and development approval has been obtained prior
24
25 634 to commencement of the study.
26

27
28 635 Local study investigator(s) will be appointed to each site (or for small units, groups of
29
30 636 sites). S/he will be responsible for the overall conduct of the study at the site and
31
32 637 compliance with the protocol and any protocol amendments.
33

34 638

35
36
37 639 **STUDY CONDUCT RESPONSIBILITIES**
38

39 640 *Protocol amendments*
40

41
42 641 Any changes in research activity, except those necessary to remove an apparent,
43
44 642 immediate hazard to the participant in the case of an urgent safety measure, will be
45
46 643 reviewed and approved by the Chief Investigator and Sponsor. Amendments to the
47
48 644 protocol will be submitted in writing to the appropriate REC and local Research and
49
50 645 Development (R&D) department for approval prior to participants being enrolled into
51
52 646 an amended protocol.
53

54
55 647 *Protocol violations and deviations*
56
57
58
59
60

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2
3 648 Investigators will not implement any deviation from the protocol without agreement
4
5 649 from the Chief Investigator and appropriate REC and R&D department approval
6
7 650 except where necessary to eliminate an immediate hazard to trial participants. In the
8
9 651 event that an Investigator needs to deviate from the protocol, the nature of and
10
11 652 reasons for the deviation will be recorded. If this necessitates a subsequent protocol
12
13 653 amendment, this will be submitted to the REC, and local R&D department for review
14
15 654 and approval if appropriate.

16
17
18 655 *Serious breach requirements*

19
20 656 A serious breach is one which is likely to effect to a significant degree (a) the safety
21
22 657 or physical or mental integrity of the participants of the trial; or b) the scientific value
23
24 658 of the trial. If a potential serious breach is identified by the Chief investigator,
25
26 659 Principal Investigator or delegates, the co-sponsors
27
28 660 (accord.seriousbreach@ed.ac.uk) will be notified within 24 hours. It will be the
29
30 661 responsibility of the co-sponsors to assess the impact of the breach on the scientific
31
32 662 value of the trial, to determine whether the incident constitutes a serious breach and,
33
34 663 if so, report it to the REC.

35
36
37 664 All violations will be assessed by the sponsor(s) to ascertain if they meet the criteria
38
39 665 for a serious breach. If the sponsor(s) deem the incident to be a violation that does
40
41 666 not constitute a serious breach from the protocol when identified, corrective and
42
43 667 preventative actions will be taken where appropriate and they will be recorded in file
44
45 668 notes, held within the TMF and ISF.

46
47 669 *Study record retention*

48
49
50 670 All study documentation will be kept for a minimum of 5 years from the protocol
51
52 671 defined end of study point. When the minimum retention period has elapsed, study
53
54 672 documentation will not be destroyed without permission from the sponsor.

55
56
57 673

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2
3 674 *End of study*
4

5 675 The end of study date was finalised in the protocol after the study commenced; the
6
7 676 agreed end of study date is 31/12/2016. The Investigators and/or the trial steering
8
9 677 committee and/or the co-sponsor(s) have the right at any time to terminate the study
10
11 678 for clinical or administrative reasons.
12

13
14 679 The end of the study will be reported to the REC within 90 days, or 15 days if the
15
16 680 study is terminated prematurely. The Investigators will inform participants of the
17
18 681 premature study closure and ensure that the appropriate follow up is arranged for all
19
20 682 participants involved. A summary report of the study will be provided to the REC and
21
22 683 Regulatory Authority within 1 year of the end of the study.
23

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25 684

26
27 685 **REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS**
28

29
30 686 Ownership of the data arising from this study resides with the study team. On
31
32 687 completion of the study, the study data will be analysed and tabulated, and a clinical
33
34 688 study report will be prepared in accordance with good clinical practice guidelines.
35
36 689 The clinical study report will be used as the basis for publication and presentation at
37
38 690 scientific meetings. Investigators have the right to publish orally or in writing the
39
40 691 results of the study. Summaries of results will also be made available to Investigators
41
42 692 for dissemination within their clinics (where appropriate and according to their
43
44 693 discretion).
45

46
47 694

48
49 695 **DISCUSSION**
50

51
52 696 The data provided by this study will inform the management of women with reduced
53
54 697 fetal movements; which has been recurrently identified by Confidential Enquiries into
55
56 698 antepartum stillbirths as suboptimal^{33 34}. This will provide much needed robust
57
58 699 evidence to determine whether increased maternal awareness of reduced fetal
59
60

1
2
3 700 movements combined with a standardised management protocol to identify acute or
4
5 701 chronic fetal compromise can reduce stillbirth ²⁷.

6
7 702

8
9
10 703 **PEER REVIEW**

11
12 704 This project has been peer reviewed internally, and was externally peer reviewed
13
14 705 during the process of securing funding from the Chief Scientist's Office of the
15
16 706 Scottish Government, Tommy's and Sands.

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21 708 **FUNDING**

22
23 709 The AFFIRM study is investigator initiated and funded by Chief Scientist Office,
24
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26
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36
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47 721

48
49 722 **CONTRIBUTIONS**

50
51 723 Contributors AEPH, CJW, SJES, CJC, SCB, MRD, SW and JEN were involved in
52
53 724 developing the trial design. AEPH, CJW, SJES, AR and JEN were involved in
54
55 725 drafting and revision of the article. CJW and AR were involved in drafting the
56
57 726 statistical aspects of the protocol. JS provided feedback on behalf of a stakeholder
58
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3 727 organisation. AEPH, CJW, SJES, CJC, SCB, JFF, MG, AH, FMM, EM, AR, MRD, JS,
4
5 728 SW and JEN were involved in preparing the overall study design. AEPH, JEN and
6
7 729 MRD prepared education videos for online training. AEPH, SJES, SJS, MG, AH,
8
9 730 FMM and JEN facilitated recruitment of sites. AEPH, CJW, SJES, CJC, SCB, JFF,
10
11 731 MG, AH, FMM, EM, AR, MRD, JS, SW and JEN will be involved in the collection,
12
13 732 management, analysis and interpretation of data and final writing of the trial report.
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17 734 **COMPETING INTERESTS**

18
19 735 None declared.
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736 **ABBREVIATIONS**

737	ACCORD	Academic and Clinical Central Office for Research & Development -
738		Joint office for University of Edinburgh and NHS Lothian
739	BMI	Body Mass Index
740	CTG	Cardiotocograph
741	CTIMP	Clinical Trial of an Investigational Medicinal Product
742	ECTU	Edinburgh Clinical Trials Unit
743	FGR	Fetal growth restriction
744	MHRA	Medicines and Healthcare products Regulatory Agency
745	NICE	National Institute for Health and Social Care Excellence
746	NIHR	National Institute for Health Research
747	NIMATS	Northern Ireland Maternity Statistics database
748	NRPS	National Perinatal Reporting System
749	ONS	Office of National Statistics
750	PSANZ	Perinatal Society of Australia and New Zealand
751	RCOG	Royal College of Obstetricians and Gynaecologists
752	R&D	Research and Development
753	REC	Research Ethics Committee
754	RFM	Reduced Fetal Movements
755	SPIMMR	Scottish Perinatal and Infant Mortality and Morbidity Report
756	TMF	Trial Master File
757	TSC	Trial Steering Committee
758	WHO	World Health Organisation
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3 882 **FIGURE LEGENDS**
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5 883 Figure 1 - Stepped wedge design. The shaded areas indicate periods in which the
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7 884 interventions are being implemented. The order in which hospital groupings
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9 885 implement the interventions will be determined via randomization.
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12 886 Figure 2 – Flow chart for the management of women presenting with reduced fetal
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14 887 movements for sites implementing the AFFIRM study. Abbreviations: AC - abdominal
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16 888 circumference, CTG- cardiotocograph, DVP - deepest vertical pool, EFW - estimated
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18 889 fetal weight, FGR - fetal growth restriction, LV - liquor volume, RFM - reduced fetal
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20 890 movement, USS - ultrasound scan.
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Hospital groupings	Months since Start of Trial								
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Woman attends with reduced fetal movements

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First episode of RFM

Recurrent RFM

24⁺⁰-26⁺⁶ weeks

27⁺⁰-36⁺⁶ weeks

37⁺⁰ weeks and more

24⁺⁰-26⁺⁶ weeks

27⁺⁰-36⁺⁶ weeks

37⁺⁰ weeks and more

Assess for risk factors for stillbirth and FGR

Assess for risk factors for stillbirth and FGR

CTG and LV normal
Consider IOL within 48h as an alternative to USS for women ≥40 weeks gestation

Assess for risk factors for stillbirth and FGR

Assess for risk factors for stillbirth and FGR

Perform CTG within 2h of presentation and LV within 12h

Confirm fetal viability OR If ≥26+0 perform CTG

Perform CTG within 2h of presentation and LV within 12h

Perform CTG within 2h and LV within 12h of presentation

Confirm fetal viability OR If ≥26+0 perform CTG

CTG abnormal or LV reduced (≤ 2cm DVP)
Individualised management plan by Senior Obstetrician

CTG Normal and LV normal
Schedule twice weekly CTG and weekly LV until next USS for EFW/AC +/- Doppler (≥ 21 days since previous USS)

Perform CTG within 2h of presentation

Perform anomaly scan if not already complete

CTG abnormal or LV reduced (≤ 2cm DVP)
Individualised management plan by Senior Obstetrician

CTG +LV Normal
USS next working day for EFW / AC +/- Doppler if ≥ 21 days since previous USS

CTG abnormal or LV reduced (≤ 2cm DVP)
Arrange delivery with input from senior obstetrician on timing and certainly within 48h

CTG +LV Normal
USS next working day for EFW / AC +/- Doppler if ≥ 21 days since previous USS

Perform anomaly scan if not already complete

EFW/AC ≤10th centile or abnormal Doppler or reduced growth velocity
Review by Senior Obstetrician

EFW/AC and LV normal on repeat USS
Return to routine care

Offer delivery
(with input from Senior Obstetrician on timing and certainly within 48h)

EFW/AC ≤10th centile or decreased growth velocity
Perform umbilical artery Doppler and review by Senior Obstetrician

EFW/AC >10th centile and normal perception of FMs
Return to original care with advice about recurrent RFM

EFW/AC ≤ 10th centile or Doppler abnormal or decreased growth velocity
Arrange delivery within 48h

EFW/AC >10th centile and normal perception of FMs
Return to original care with advice about recurrent RFM

If high-risk for FGR arrange serial growth USS as per local policy / RCOG guideline

The RCOG guideline for the management of the Small for Gestational Age fetus should be consulted. Consider delivery by 37 weeks for women with suspected FGR.



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___ Page 1 ___
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___ Page 4 ___
	2b	All items from the World Health Organization Trial Registration Data Set	_Included throughout protocol_
Protocol version	3	Date and version identifier	___ Page 4 ___
Funding	4	Sources and types of financial, material, and other support	___ Page 28 ___
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_Names and affiliations Page 1 and 2; Contributions Page 28_
	5b	Name and contact information for the trial sponsor	___ Page 24 ___
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_Not applicable_

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3		5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
4			___Page 24___
5			
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8	Introduction		
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10	Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
11			__Pages 5-11__
12		6b	Explanation for choice of comparators
13			__Pages 8-9__
14	Objectives	7	Specific objectives or hypotheses
15			__Pages 11-12__
16	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
17			__Pages 13- 14 and Figure 1__
18			
19			
20	Methods: Participants, interventions, and outcomes		
21			
22	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
23			__Pages 13 & 16__
24			
25	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
26			__Pages 14-15__
27			
28	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
29			__Pages 17-18 and Figure 2__
30		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
31			__Not applicable in AFFIRM trial__
32		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
33			__Pages 17-18__
34		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
35			__Not applicable__
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3	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	__Pages 12-13__
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8	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	__Randomisation by site explained in Figure 1 and Pages 13-14__
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14	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	__Pages 21-22__
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17	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	__Page 22__
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20	Methods: Assignment of interventions (for controlled trials)			
21	Allocation:			
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23	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	__Page 17__
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29	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	__Page 17__
30				
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33	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	__Page 17__
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36	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	__Page 17__
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39		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_ Not applicable in AFFIRM study__
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Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	__Pages 18-21__
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	__Not applicable__
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	__Pages 19-20__
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	__Pages 22-23__
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	__Page 23__
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	__Pages 22-23__

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_DMC not required, explanation Pg 24__
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	__Pages 18, 25-26__
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	__Page 24__
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	__Page 13__

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3 **Ethics and dissemination**
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5 Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	__Page 25__
6			
7			
8 Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	__Page 25__
9			
10			
11			
12 Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	__Page 25__
13			
14			
15			
16	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	__Not applicable__
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19 Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	__Page 20__
20			
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22 Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	__Page 29__
23			
24			
25 Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	__Page 27__
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27			
28 Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	__Page 24__
29			
30			
31 Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	__Page 27__
32			
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35			
36	31b	Authorship eligibility guidelines and any intended use of professional writers	__Page 28__
37			
38	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	__Not applicable__
39			

40 **Appendices**
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Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_Not Applicable__
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_Not Applicable__

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.

peer review only

WHO TO CONTACT IF YOU ARE CONCERNED:
(space for sticky with local contact information)



APS Group Scotland
DPPAS33137
Version 3 March 2015



In touch with **YOUR BABY**

A guide to your baby's
movements during
pregnancy



For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

Why are my baby's movements important?

Why are we asking women to get to know their baby's movements?

One of the easiest ways to tell if your baby is healthy is to be aware of how much he or she is moving. Every baby is different and we are asking women to take time to become familiar with their baby's own individual pattern of movements. A reduction or change in **your** baby's movements is what is important.

What can affect my baby's movements?

You are less likely to be aware of your baby's movements when active or busy. Some drugs e.g. strong pain relief or sedatives can get into an unborn baby's circulation and affect the movements. Alcohol and smoking (active and passive smoking) may also affect the baby.

Why are my baby's movements important?

If you notice your baby is moving less than usual, or the pattern of movements has changed, this could be the first sign that your baby may not be well or is not growing properly in the womb. Research has shown that a reduction in the baby's movements may indicate an increased risk of stillbirth. You may hear your midwife or doctor referring to 'reduced fetal movement', or RFM for short.

What are the risks of stillbirth?

Stillbirth affects one in 200 babies after 24 weeks gestation and is one of the most common of the serious complications of pregnancy, affecting the lives of around 4,000 families every year in the UK.

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One of the easiest ways to tell if your baby is healthy is to see how much he or she is moving. This booklet tells you what to look out for during your pregnancy.



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Every baby is different. It is good to get to know your baby's own movements and the pattern of their sleeping and waking and report to us if you notice a reduction in these movements.

18-24
WEEKS



24-36
WEEKS



Most women begin to feel their baby move between 18-24 weeks. At first it may feel like 'bubbles', 'flutterings' or 'like trapped wind'. These are often very short and stop and start. It might take you a little while to be sure what you are feeling. But you will soon get to know the feelings. If this is your second baby, you will know what to look out for and may recognise your baby moving sooner.

Everyone is different when it comes to their movements. There are many reasons you might not feel movements as early as you expect. This includes your body weight, the position of your baby and the location of your placenta. What is important is your baby is growing well. Your midwife will be able to discuss this with you further at your 22 week check.

Try to get to know the times of the day when you are most likely to feel your baby move.



You will have your own way of describing your baby's own movements. Women often describe their baby's movements as 'rolling', 'kicking', 'pushing', 'jabs', 'elbowing' and 'stretches'.

Between 24-36 weeks you will start to recognise your baby's movements more quickly and become more used to the feeling. It is usually easier to feel your baby's movements when you are lying down, e.g. at night time. It is harder to feel your baby move when you are on your feet and moving around.

Try to get to know the times of the day you are most likely to feel your baby move. This will help you to know if he or she is moving less than normal or if movements have stopped.

Occasionally your baby will get hiccups. These do not count as movements. If you are unsure what you should expect when your baby hiccups, speak to your midwife.

BMJ Open

Can Promoting Awareness of Fetal movements and Focussing Interventions Reduce Fetal Mortality? - A stepped wedge cluster randomised trial (AFFIRM)

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-014813.R1
Article Type:	Protocol
Date Submitted by the Author:	10-Jan-2017
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Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Research methods
Keywords:	Reduced Fetal Movements, Perinatal Mortality, Stillbirth, Neonatal Death, Fetal Growth Restriction

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3 **1 Study Protocol**
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5 2 Can Promoting Awareness of Fetal movements and Focussing Interventions Reduce
6 3 Fetal Mortality? - A stepped wedge cluster randomised trial (AFFIRM)
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2
3 40 **Abstract**
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5 41 *Background* - In 2013, the stillbirth rate in the UK was 4.2 per 1,000 live births,
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7 42 ranking 24th out of 49 high-income countries, with an annual rate of reduction of only
8
9 43 1.4% per year. The majority of stillbirths occur in normally formed infants, with
10
11 44 (retrospective) evidence of placental insufficiency the commonest clinical finding.
12
13 45 Maternal perception of reduced fetal movements (RFM) is associated with placental
14
15 46 insufficiency and increased risk of subsequent stillbirth.
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17
18 47 This study will test the hypothesis that the introduction of a package of care to
19
20 48 increase women's awareness of the need for prompt reporting of RFM and
21
22 49 standardised management to identify fetal compromise with timely delivery in
23
24 50 confirmed cases, will reduce the rate of stillbirth. Following the introduction of a
25
26 51 similar intervention in Norway the odds of stillbirth fell by 30%, but the efficacy of this
27
28 52 intervention (and possible adverse effects and implications for service delivery) have
29
30 53 not been tested in a randomised trial.
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33 54 *Methods* - We describe a stepped wedge cluster trial design, in which participating
34
35 55 hospitals in the UK and Ireland will be randomized to the timing of introduction of the
36
37 56 care package. Outcomes (including the primary outcome of stillbirth) will be derived
38
39 57 from detailed routinely collected maternity data, allowing us to robustly test our
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41 58 hypothesis. The degree of implementation of the intervention will be assessed in
42
43 59 each site. A nested qualitative study will examine the acceptability of the intervention
44
45 60 to women and health care providers and identify process issues including barriers to
46
47 61 implementation.
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50 62 *Discussion* - The data provided by this study will inform the management of women
51
52 63 with RFM; which has been recurrently identified as suboptimal in cases of stillbirth.
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54 64 This will provide robust evidence to determine whether increased maternal
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56 65 awareness of RFM combined with a standardised management protocol to identify
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58 66 acute or chronic fetal compromise can reduce stillbirth.
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3 67 *Trial Registration*

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5 68 www.clinicaltrials.gov NCT01777022

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8 69 *Version*

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10 70 Protocol Version 4.2, 19th December 2016

11
12 71 *Keywords*

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15 72 Reduced Fetal Movements; Perinatal Mortality; Stillbirth; Neonatal Death; Fetal
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17 73 Growth Restriction.

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22 75 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

23
24 76 • This trial directly addresses the need for studies of the information given to
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26 77 women regarding fetal movements and the subsequent management of reduced
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28 78 fetal movements identified by Confidential Enquiries into Antepartum Stillbirths,
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30 79 Systematic Reviews and the Stillbirth Priority Setting Partnership.

31
32 80 • A stepped-wedge cluster trial design in combination with routinely collected
33
34 81 maternity data allows the trial to be adequately powered to detect a difference in
35
36 82 stillbirth as a primary outcome.

37
38 83 • The pragmatic nature of the study represents the potential impact of the
39
40 84 introduction of such standardised care into clinical practice.

41
42 85 • The nested qualitative study will provide information regarding the acceptability
43
44 86 of the intervention and identify barriers and facilitators to its adoption.

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46 87 • The lack of information on resource use before and throughout the study period
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48 88 limits the ability to understand the consequences of the intervention on maternity
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50 89 unit workload.

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3 92 **INTRODUCTION**
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5 93 *Stillbirth*
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8 94 Stillbirth, defined in the UK as a baby with no signs of life after 24 weeks of completed
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10 95 pregnancy ¹, remains the major cause of perinatal mortality in high-income
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12 96 environments, with a recent series of papers in the Lancet on stillbirth issue calling for
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14 97 renewed action in this area ². There is no single “cause” of stillbirth, and a significant
15
16 98 proportion of stillbirths remain unexplained, but fetal growth restriction, maternal
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18 99 hypertension and low socioeconomic status are amongst the identifiable risk factors ³.
19
20 100 The concept that more can be done to reduce stillbirth in the UK and Ireland is
21
22 101 supported by data showing a marked variation in rates between resource rich
23
24 102 countries, when similar definitions of stillbirth are used ². Notably, the UK has a higher
25
26 103 rate than comparable resource rich countries such as Germany, Netherlands, New
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28 104 Zealand and Norway with rates in the UK some 50% greater than those of the
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30 105 Netherlands. Disappointingly, the annual rate of reduction in stillbirth from 2000 to
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32 106 2014 in the UK was only 1.4% compared to 6.8% in the Netherlands and 2.8% in New
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34 107 Zealand ². Rates of stillbirth in Scotland (3.7 per 1,000 births in 2014) and Ireland, at
35
36 108 (4.4 per 1,000 livebirths in 2013) are similar to rates in England and Wales at 4.2 per
37
38 109 1,000 livebirths (England and Wales, 2014) ⁴. The reduction of avoidable harm for
39
40 110 women and babies is viewed as a major priority for Government and its agencies
41
42 111 throughout the UK and Ireland. Consequently, several initiatives have been
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44 112 developed by national governments in the UK and Ireland including the Scottish
45
46 113 Government Stillbirth Working Group, NHS England Saving Babies’ Lives Care
47
48 114 Bundle and the Welsh Assembly 1000 Lives Plus strategy. These strategies have
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50 115 identified the need for better evidence to guide efforts to prevent stillbirths.
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52
53 116 Using a robust priority setting strategy ⁵ the Lancet Stillbirth’s series steering
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55 117 committee identified issues around detection and management of reduced fetal
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57 118 movements (RFM) amongst the top ten key research questions on prevention and
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3 119 management of stillbirth⁶. This was confirmed in the UK-based Stillbirth Priority
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5 120 Setting partnership involving over 1,700 parents and professionals which identified
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7 121 two relevant issues among the highest ranked research questions regarding stillbirth:
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9 122 i) which investigations identify a fetus at risk of stillbirth after a mother believes she
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11 123 has experienced reduced fetal movements? and ii) would more accessible evidence-
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13 124 based information on signs and symptoms of stillbirth risk, designed to empower
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15 125 women to raise concerns with healthcare professionals, reduce the incidence of
16
17 126 stillbirth?⁷ Thus, RFM has been identified as a highly-relevant area of study by
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19 127 parents, professionals and researchers.
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21 128

22 23 129 *Reduced Fetal Movements, Stillbirth and Placental Insufficiency*

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25
26 130 There is a clear association between maternal perception of RFM and late stillbirth
27
28 131 dating back over four decades⁸. In a recent series of 2,000 women, the adjusted OR
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30 132 (95% CI) of late stillbirth in women with RFM (compared with controls) was 2.37
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32 133 (1.29-4.35)⁹. One international study of 1,714 women who experienced a stillbirth
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34 134 found that 30% had noted significant RFM prior to the diagnosis of stillbirth¹⁰.
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36 135 Although the mechanisms have not been fully delineated, it is likely that RFM and
37
38 136 stillbirth are linked by a common pathology, that of placental dysfunction¹¹. There is
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40 137 good evidence linking placental dysfunction and RFM. Compared to controls with an
41
42 138 active fetus women who have fewer fetal movements on ultrasound scan immediately
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44 139 prior to caesarean section are more likely to have umbilical cord gas measurements
45
46 140 indicative of acidaemia, hypoxaemia, and hypercapnia¹². Women delivering within
47
48 141 one week of an episode of RFM show differences in placental structure and function
49
50 142 which are reminiscent of those seen in fetal growth restriction (FGR) and stillbirth^{13 14}.
51
52 143 Additionally, the odds of fetal growth restriction (FGR, defined as being at less than
53
54 144 the 10th centile for gestation adjusted birthweight) were greater in women with RFM
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56 145 compared with controls (adjusted OR 1.6, 95% CI 1.1–2.2¹⁵). Taken together these
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3 146 data are strong evidence that placental dysfunction is associated with RFM, and a
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5 147 causative pathway seems likely.

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7 148 The evidence linking placental dysfunction and stillbirth is even stronger; a systematic
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9 149 review of placental pathology in stillbirths described abnormalities in up to 65% of
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11 150 cases ¹⁶. Amongst the 291 stillbirths in Scotland in 2010, 137 (47%) had evidence of
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13 151 placental dysfunction ¹⁷. Given that the placenta was examined in only 80% of
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15 152 stillbirths, the true prevalence of placental dysfunction is likely to be higher. In
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17 153 addition, between 20%-40% of stillborn babies are reported to have FGR, as defined
18
19 154 by a birthweight less than the 10th centile ¹⁸. Additionally, the Lancet report notes that
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21 155 “placental pathologies accounted for one in four deaths across all gestational ages,
22
23 156 and were contributory or causal in more than half of cases” ⁶. Given that stillbirth is
24
25 157 strongly related to placental dysfunction, and RFM is a “biomarker” of placental
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27 158 dysfunction then better management of women presenting with RFM focussing on the
28
29 159 detection of placental dysfunction might reduce the risk of stillbirth.

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33 161 *Formal Fetal Movement Counting*

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35 162 Although prenatal detection of FGR is improved by fetal movement counting ¹⁹, a
36
37 163 systematic review ²⁰, and a large and influential cluster randomised trial (which
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39 164 dominates the systematic review) showed that routine fetal movement counting using
40
41 165 the count to ten charts had no effect on perinatal mortality ²¹. Thus, the National
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43 166 Institute for Health and Social Care Excellence (NICE) recommended that “Routine
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45 167 formal fetal movement counting should not be offered” ²². Importantly, the large
46
47 168 cluster randomised trial tested a specific alarm limit for RFM, but did not recommend
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49 169 a specific management strategy for women who did present with RFM. There were
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51 170 two important observations from this study, firstly that in both groups the perinatal
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53 171 mortality rate was lower than contemporary or subsequent periods in the UK and
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55 172 secondly that more women in the fetal movement counting arm came in with a live
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57 173 baby who subsequently died compared with the control arm (19 vs 11), suggesting

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3 174 that one reason the strategy failed to reduce perinatal mortality was inadequate
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5 175 investigation and management of those presenting with RFM ²¹.

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9 177 *Optimal strategy for determining RFM to prompt maternal presentation to the*
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11 178 *maternity service*

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13 179 Maternal concern about RFM is a common reason to contact maternity services with
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15 180 between 6-15% of women presenting during the third trimester.^{23 24} Nevertheless,
16
17 181 delays in reporting RFM to maternity care providers may increase the risk of adverse
18
19 182 outcome.^{25 26} The lack of good-quality information given to women about fetal
20
21 183 movements has been highlighted as an example of suboptimal care in Confidential
22
23 184 Enquiries into Antepartum Stillbirth.^{27 28} Qualitative studies suggest that women
24
25 185 frequently perceive RFM two days prior to the diagnosis of fetal death, and in some
26
27 186 cases contractions were misinterpreted as fetal movements.²⁹ Therefore, giving
28
29 187 information to women regarding fetal movements and when they should be
30
31 188 concerned about RFM is a key component of an intervention to reduce stillbirth.

32
33 189 However, giving clear information about RFM can be challenging as there is no
34
35 190 uniform threshold of fetal movements below which perinatal morbidity increases ²⁴,
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37 191 and no evidence that a specific threshold performs better than maternal perception of
38
39 192 reduced fetal movements alone ⁸. Current guidelines from the RCOG and PSANZ ³⁰
40
41 193 ³¹, informed by a large Norwegian study ³² suggest that it is *maternal perception* of
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43 194 decreased fetal movement which is important. Therefore, information for pregnant
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45 195 women in this study (shown in Supplementary File 1) described the importance of
46
47 196 fetal movements, the need to get to know normal fetal activity, how fetal movements
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49 197 change in late pregnancy and who to contact if the mother perceives RFM. The
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51 198 educational package aimed to ensure that these messages were reinforced by staff
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53 199 behaviour at antenatal contacts.

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58 201 *Optimal strategy for investigation and management of women presenting with RFM.*
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3 202 A recent systematic review found there are no proven strategies for the investigation
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5 203 and management of women presenting with RFM ³³. Cardiotocography (CTG) is
6
7 204 routinely used to ascertain fetal wellbeing, and it is the cornerstone of the RCOG
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9 205 guideline ³¹. However, data from Norway, suggests that ultrasound assessment of
10
11 206 fetal size is often the most helpful investigation, performing well on both an absolute
12
13 207 basis, and compared with other interventions ³⁴. In a series of over 3,000 women with
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15 208 RFM, ultrasound (including measurement of fetal biometry and liquor volume) was
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17 209 found to be useful in detecting abnormalities in 11.6% of scans. In 71% of women in
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19 210 whom an abnormality was found, ultrasound was the only technique that detected an
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21 211 abnormality. Additionally, 85% of abnormalities detected by ultrasound, were
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23 212 important in informing the clinical management of the woman ³⁴. These data are
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25 213 supported by a smaller UK study which found that abnormalities detected on CTG or
26
27 214 ultrasound scan were most strongly associated with adverse outcome in women with
28
29 215 RFM, with identification of abnormal estimated fetal growth centile on scan being the
30
31 216 test most highly predictive of poor outcome ³⁵. Perhaps this is not surprising, given the
32
33 217 strong association between RFM and placental dysfunction and the central
34
35 218 importance of ultrasound in the identification and management of small for gestational
36
37 219 age babies ³⁶. Given these data, it is concerning that a survey of clinicians in Scotland
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39 220 showed that fewer than 5% would routinely refer women with RFM for ultrasound
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41 221 examination (unpublished data from June 2012), and a survey of 223 UK midwives
42
43 222 and obstetricians described that 17.9% of respondents would perform an ultrasound
44
45 223 scan ³⁷. These views of clinicians may reflect the variable quality of local guidelines,
46
47 224 which are frequently not based on national recommendations, even those for which
48
49 225 there is strong evidence ³⁸. The variation in information given to women and
50
51 226 subsequent management of RFM has been highlighted as sources of suboptimal care
52
53 227 in two confidential enquiries into antepartum stillbirth ^{27 28}. Therefore, we believe that
54
55 228 current investigation of women presenting with RFM is inadequate, hence using the
56
57 229 best available evidence, we have drafted what we consider to be a robust evaluation
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3 230 protocol for investigation of women with RFM.
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5 231 *Potentially efficacy of a package of intervention for RFM*
6
7 232 Supportive data for the package of interventions used in this study (information for
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9 233 women and standardised management protocol) comes from a large observational
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11 234 “clinical quality improvement study” in Norway which found a significant fall in rates of
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13 235 stillbirth (from 3.0/1,000 to 2.0/1,000 [OR 0.67 95% CI 0.48–0.93]) after the
14
15 236 introduction of an intervention package consisting of written information for women
16
17 237 about awareness of RFM combined with consensus guidelines for health
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19 238 professionals about their management ³². Although this study was not randomised,
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21 239 and therefore constitutes only level II-3 evidence, it has informed recommendations
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23 240 from the Royal College of Obstetricians and Gynaecologists (RCOG) and Perinatal
24
25 241 Society of Australia and New Zealand (PSANZ) that “women should be advised to be
26
27 242 aware of their baby’s individual pattern of movements and that if they are concerned
28
29 243 about a reduction in or cessation of fetal movementsthey should contact their
30
31 244 maternity unit” ^{30 31}. Following initial publication of the Norwegian study, a re-analysis
32
33 245 was required as discrepancies between stillbirth rates in the study and the Medical
34
35 246 Birth Registry of Norway were identified. This reanalysis found the reduction in
36
37 247 stillbirth rates was of borderline statistical significance (OR 0.72, 95% CI 0.50-1.03).
38
39 248 The authors concluded that further studies were needed to determine whether this
40
41 249 approach was associated with a reduction in stillbirth ³⁹.
42
43 250 Importantly, in the Norwegian study, there was no increase in the proportion of
44
45 251 women who presented with RFM when rates were compared before and after the
46
47 252 intervention ³². However, women with RFM presented significantly earlier to hospital
48
49 253 than they had hitherto, potentially allowing time for intervention to reduce perinatal
50
51 254 mortality. These data suggest that a package of interventions encouraging women
52
53 255 with RFM to present early to hospital, combined with a structured approach to their
54
55 256 management might reduce rates of stillbirth without contributing to a large increase in
56
57 257 admissions antenatally.
58
59
60

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3 258

4
5 259 *Potential harms of a package of care around increased awareness and optimised*
6
7 260 *management of RFM*

8
9
10 261 Any clinical intervention which aims to improve outcomes also has the ability to do
11
12 262 harm. Thus, it is essential that the intervention proposed is rigorously evaluated using
13
14 263 the gold standard technique of a randomised trial, rather than being introduced as a
15
16 264 service development. When the study began, there was a small window of
17
18 265 opportunity to do this, as the enthusiasm to improve current management of RFM is
19
20 266 such that routine introduction of the package of care is unlikely to be delayed much
21
22 267 further than the current scheduled end date of this study. Possible harms of a
23
24 268 package of care consisting of a management plan for identification and delivery of the
25
26 269 “at risk” fetus, together with strategies for increasing pregnant women’s awareness of
27
28 270 the need to report early include increased maternal anxiety and increased
29
30 271 intervention (including hospital admission, induction of labour and Caesarean section)
31
32 272 which itself is associated with pregnancy related complications. The available
33
34 273 evidence is reassuring on some of these issues. A systematic review of 23
35
36 274 publications from 16 studies found three studies involving 2,030 women addressing
37
38 275 maternal concern and an additional three studies involving 1,468 women investigating
39
40 276 maternal-fetal attachment. These demonstrated no evidence of increased maternal
41
42 277 anxiety and results regarding maternal-fetal attachment were discordant.⁴⁰ In the
43
44 278 Norwegian service development study, the package of care increased rates of follow
45
46 279 up of women, but there was no increase in admissions overall, admissions for
47
48 280 induction or admissions for emergency caesarean section ³² – again, whilst
49
50 281 reassuring these outcomes require formal evaluation in a randomised and relevant
51
52 282 setting to the UK and Republic of Ireland. The final possible harm of the package is
53
54 283 around increased resource use, and the opportunity cost of focussing on RFM rather
55
56 284 than other potential methods to prevent stillbirth.

285

RATIONALE

The aim of this study is to test the hypothesis that a package of interventions consisting of strategies for increasing pregnant women's awareness of the need to report early when they perceive a reduction in fetal movements, followed with a management plan for identification and delivery of the "at risk" fetus in such women, will reduce rates of stillbirth.

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STUDY OBJECTIVES*Primary Objective*

The primary objective is to answer the research question 'Does the introduction of a protocol for detection and management of decreased fetal movements reduce rates of stillbirth?' The secondary objectives are to answer the following research questions:

- What is the effect of the intervention on rates of caesarean section and induction of labour?
- What is the effect of the intervention on rates of admission to the neonatal intensive care unit?
- What is the effect of the intervention on the proportion of women with FGR remaining undelivered by 40 weeks gestation?
- What is the acceptability of such a package of care to pregnant women and their health care providers?
- What other process outcomes are influenced by the intervention, such as health care provider/patient interactions?

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1
2
3 310 **ENDPOINTS**
4

5 311 *Primary Outcome*
6

7
8 312 The primary endpoint is stillbirth (antepartum and intrapartum). We will use the UK
9
10 313 definition of stillbirth which is “a baby delivered without signs of life after 23⁺⁶ weeks”
11
12 314 ⁴. Where gestation is uncertain we will include all babies with a birth weight of 500g
13
14 315 or more.
15

16 316 *Secondary Endpoints*
17

18
19 317 Other measures of perinatal mortality including:
20

- 21 318 • Stillbirth at 37 weeks gestation and above
22
23
24 319 • Stillbirth at 28 weeks gestation and above (WHO definition of stillbirth)
25
26
27 320 • Stillbirth at 22 weeks gestation and above (international stillbirth alliance
28
29 321 definition)
30
31 322 • Stillbirths amongst normally formed infants of 22 weeks gestation and above,
32
33 323 24 weeks gestation and above, 28 weeks gestation and above and 37 weeks
34
35 324 gestation and above.
36
37
38 325 • Perinatal mortality (defined as stillbirth at 24 weeks gestation and above and
39
40 326 deaths in the first seven days of life)
41
42
43 327 • Rates of caesarean section
44
45
46 328 • Rates of induction of labour (for any indication)
47
48 329 • Rates of elective delivery (induction of labour and caesarean section prior to
49
50 330 the onset of labour) overall
51
52
53 331 • Rates of induction of labour at 39 weeks gestation or later
54
55
56 332 • Mean gestation at induction of labour
57
58 333 • Rates of admission to the neonatal unit (and their reasons)
59
60

- 1
2
3 334 • Rates of admission to the neonatal unit for more than 48 hours
4
5
6 335 • Rates of admission to the neonatal unit for term babies (those born at 37
7
8 336 weeks 0 days or greater)
9
10 337 • Proportion of infants with fetal growth restriction (less than the 5th centile,
11
12 338 customised for gender) remaining undelivered at or after 40 weeks gestation
13
14 339 • Birthweight centile (according to the Intergrowth birthweight centile calculator
15
16 340 at <https://intergrowth21.tghn.org>)
17
18
19 341 • Rates of spontaneous vaginal delivery
20
21
22 342 Other secondary outcomes are the baby parameters:
23
24 343 • Gestation at birth
25
26
27 344 • Proportion of babies born preterm (<37 weeks gestation)
28
29
30 345 • Gender of the baby
31
32 346 • Birthweight of the baby
33
34
35 347 • Apgar score at 5 minutes
36
37 348 • Proportion of babies with 5 minute Apgar score < 7
38
39
40 349 • Proportion of babies with 5 minute Apgar score < 4
41
42
43 350 • Resuscitation required at birth
44

45 351 We will also collect the following data: maternal age, maternity unit of delivery,
46
47 352 birthweight, gestation of delivery, parity, gestation, sex, smoking (current and ever),
48
49 353 maternal body mass index (BMI), number of babies (one or more), ethnicity (to allow
50
51 354 a customised birthweight centile to be generated), method of delivery, deprivation
52
53 355 category (where available) and other neonatal variables including Apgar score and
54
55 356 encephalopathy. Adjustment will be made for the following variables: (maternal age,
56
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1
2
3 357 maternity unit of delivery, parity, smoking status, maternal BMI, number of babies
4
5 358 [one or more] and ethnicity)

6
7 359

8
9
10 360 **STUDY DESIGN**

11
12 361 This is a multicentre, stepped wedge cluster randomised trial of a package of care
13
14 362 consisting of a management plan for identification and delivery of the 'at risk' fetus,
15
16 363 together with strategies for increasing pregnant women's awareness of the need to
17
18 364 report RFM early. The trial developed from a planned quality improvement project
19
20 365 proposed by the Scottish Government to reduce stillbirths. This was planned to
21
22 366 emphasise the importance of fetal movement monitoring and was to be rolled out to
23
24 367 all NHS maternity units in Scotland. However, prior to this change it was agreed that
25
26 368 the roll out could be performed in such a way as to allow the assessment of the effect
27
28 369 of the intervention, the stepped-wedge design would be the natural choice in this
29
30 370 circumstance.

31
32
33 371 The study will take place in participating hospitals in the UK and Ireland (a complete
34
35 372 list is available <http://www.crh.ed.ac.uk/affirm/randomised-hospitals/>). A nested
36
37 373 qualitative study will examine the acceptability of the intervention to patients and
38
39 374 health care providers and identify process issues (barriers to implementation).
40
41 375 Clinical audit (detailed in supplementary information 2) conducted after the change in
42
43 376 practice will be used to determine the effect of interventions on process outcomes
44
45 377 (e.g. number of women presenting with reduced fetal movements, interval between
46
47 378 perceiving reduced fetal movements and presentation to hospital, number of
48
49 379 ultrasound scans, number of admissions for induction of labour). A diagram indicating
50
51 380 randomisation of hospital groupings in the stepped wedge design is shown in Figure
52
53 381 1.

1
2
3 382 The interventions will be introduced over a 32 month period. Data will be collected
4
5 383 over a 36 month period. Data in the 'active phase' after introduction of the
6
7 384 intervention will be compared to data in the 'control phase' – the period during which
8
9 385 usual care processes in study sites are followed from study start to the time of
10
11 386 introduction of the intervention. Given that it will take individual units some time (a) to
12
13 387 effect change in management in their unit from time of introduction of the intervention
14
15 388 and (b) that it will take some time for this change in practice to impact on clinical
16
17 389 outcomes, we plan a “washout” period of two months after the introduction of the
18
19 390 intervention during which data will not be included in either group for analysis (Figure
20
21 391 1). Data will be collected four months after the last birth, a further two months has
22
23 392 been included for data analysis, giving a total study duration of 42 months.
24
25
26
27

28 394 **STUDY POPULATION**

29 395 *Number of participants*

30
31
32
33 396 Participants will be those delivering at all the sites over the study period (36 months).
34
35 397 All eligible women will be recruited to the cluster randomised controlled trial. Based
36
37 398 on previous delivery numbers, after accounting for a washout period of two months
38
39 399 (and assuming no withdrawals or losses to follow up) this is estimated to be a total of
40
41 400 around 143,140 women per annum. A subset of around 30 participating women and
42
43 401 30 midwives, sonographers and obstetricians will be recruited to the nested
44
45 402 qualitative study, which is based in the Scottish sites.

46 403 *Inclusion criteria*

47
48
49
50 404 We will include all women delivering at one of the participating maternity units for the
51
52 405 duration of the study. Women who have been seen at any of the maternity units but
53
54 406 who deliver at home will not be included. The duration of the study will be 42 months
55
56
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1
2
3 407 from the start of the trial (01/02/2014). For practical reasons, participants for the
4
5 408 nested qualitative study will be recruited from the participating units in Scotland.

6
7 409 *Exclusion criteria*

8
9 410 We will exclude women as follows:

- 10
11
12 411 • Women for whom data on delivery outcomes is still unavailable four months after
13
14 412 the date of delivery
15
16
17 413 • Women delivering in the “washout” period in each unit.

18
19
20 414 Members of the trial management group and participants who do not
21
22 415 speak/understand English will be excluded from participating in the nested qualitative
23
24 416 study.

25
26 417 *Identifying participants*

27
28
29 418 Women will be identified from those whose data is included in routine data returns
30
31 419 from each unit. Potential participants for the nested qualitative study will be identified
32
33 420 from those attending antenatal clinics in participating hospitals, and/or local staff.

34
35 421 *Consenting participants*

36
37
38 422 The main study is a stepped wedge cluster randomised trial of a package of care
39
40 423 which would be introduced in many of the participating units regardless of whether
41
42 424 the trial was on-going or not and the trial uses only routinely collected data on
43
44 425 participants. The ethics committee indicated that formal individual patient consent is
45
46 426 not necessary for the main trial. Participants in the nested qualitative study will be
47
48 427 asked for individual consent.

49
50 428 *Screening for eligibility*

51
52
53 429 As participants are not directly recruited we will not perform any specific screening
54
55 430 tests for this aspect of this project. Participants for the nested qualitative study will
56
57 431 be: (i) Pregnant women attending hospitals who are participating in the main trial in

1
2
3 432 Scotland. Purposive sampling will ensure that the final sample set includes women
4
5 433 who have and who have not experienced RFM, both before and after the introduction
6
7 434 of the intervention; (ii) Hospital staff (including midwives, ultrasonographers and
8
9 435 obstetricians/radiologists) working in participating hospitals in Scotland. There will be
10
11 436 no specific screening tests for eligibility for the nested qualitative study, except that
12
13 437 women who have experienced a stillbirth in the index pregnancy will not be
14
15 438 approached.

16
17
18 439 *Ineligible and non-recruited participants*

19
20 440 Potential participants for the nested qualitative study who are not approached or who
21
22 441 decline will have no specific interventions / procedures.

23
24
25 442 *Withdrawal of Study Participants*

26
27 443 The nature of a cluster randomised study is such that it is not possible for the
28
29 444 participant to withdraw from the “cluster” unless she changes maternity unit part way
30
31 445 through her pregnancy. We plan to collect routinely recorded anonymised data;
32
33 446 patients have the right to opt out of having their data used – if this happens their data
34
35 447 would be excluded from the study database (e.g. under the Confidentiality and
36
37 448 Security advisory Group Report 2002 and the Data Protection Act (1998)
38
39 449 requirements for fair processing of data). Participants in the nested qualitative study
40
41 450 who wish to withdraw will be allowed to do so. Their data will be retained and used,
42
43 451 unless they additionally indicate that they wish to withdraw their data.

44
45
46 452 **RANDOMISATION**

47
48
49 453 *Randomisation Procedures*

50
51 454 This is a cluster-randomised, stepped-wedge design trial wherein maternity units
52
53 455 rather than individual patients are randomised. All units will implement the fetal
54
55 456 movement monitoring intervention at some point during the trial; the random element
56
57 457 is the time point at which this will occur, the so-called “step” of the stepped-wedge

1
2
3 458 design. Participating maternity units will be blinded to their randomly allocated time
4
5 459 point until the time this is required to be revealed to enable the necessary training in
6
7 460 the implementation of the intervention to be delivered. Primary and secondary
8
9 461 outcomes of the trial will be gathered in a blinded manner via routinely collected data
10
11 462 sources.

12
13 463 Maternity units which are in close proximity to each other will be grouped for the
14
15 464 purposes of randomisation. This will assist with the feasibility of delivering the training
16
17 465 for and implementation of the intervention. Furthermore, this local synchronisation of
18
19 466 the intervention implementation will minimise the chances of contamination
20
21 467 (introduction of the intervention prematurely) from maternity units which have already
22
23 468 implemented the intervention to those not yet randomised.

24
25
26 469 The order in which the groups of maternity units step in to implement the intervention
27
28 470 will be determined by computer generated random numbers from a uniform
29
30 471 distribution. The randomisation list will be held by the Edinburgh Clinical Trials Unit
31
32 472 (ECTU). The identities of the research team staff whose roles in the trial require them
33
34 473 to be unblinded to randomisation codes will be recorded in the trial master file (TMF).

35 36 37 474 *Treatment Allocation*

38
39 475 Participating sites will be randomised to the intervention or conventional clinical
40
41 476 management. All units will be providing conventional treatment at baseline according
42
43 477 to local practice – this is the treatment established before the study starts. Sites will
44
45 478 be randomised to “active” treatment in turn as described above. Active treatment will
46
47 479 consist of a package of care consisting of a management plan for identification and
48
49 480 delivery of the ‘at risk’ fetus, together with strategies for increasing pregnant women’s
50
51 481 awareness of the need to report RFM early. The recommended management plan for
52
53 482 identification and delivery of the “at risk” fetus is shown in Figure 2. Practice change
54
55 483 in the active units will be achieved by: (i) written/email information to all clinicians
56
57 484 (doctors, midwives and ultrasonographers) in each unit about the study protocol and
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1
2
3 485 amendment of the local protocol for Reduced Fetal Movements (RFM) to that of the
4
5 486 study protocol; (ii) a short web-based training package taking approximately one hour
6
7 487 to complete for all clinicians in each centre and (iii) training /information sessions to
8
9 488 run in each unit and (iv) posters in each unit to describe the practice change.
10
11 489 Strategies for encouraging clinicians to increase pregnant women's awareness of
12
13 490 fetal movement will include all the above and also a fetal movement leaflet for
14
15 491 pregnant women (shown in Supplementary Information 1). The Norwegian quality
16
17 492 improvement study showed inconclusive results regarding the effect of the
18
19 493 intervention in non-European women.⁴¹ To attempt to address this, the AFFIRM
20
21 494 information leaflet was available in 12 languages including: Arabic, Bengali, English,
22
23 495 Hindi, Hungarian, Latvian, Lithuanian, Mandarin, Polish, Russian and Urdu.
24
25 496 Furthermore, by including staff education which highlighted the need to ask women
26
27 497 about fetal movements in routine antenatal consultations as many women as
28
29 498 possible should have received information about what to do if they perceive RFM.
30
31
32 499 Once units have begun active treatment it is not anticipated that they will return to
33
34 500 conventional treatment. We will conduct an audit of women presenting with reduced
35
36 501 fetal movements and assess the proportion of staff completing the online training to
37
38 502 assess the extent to which sites have followed the intervention plan. Units will be
39
40 503 informed about treatment allocation as near as possible to the implementation of the
41
42 504 "active" treatment. For practical purposes, we anticipate that each unit will need
43
44 505 around three months' notice before the "active" treatment is introduced, hence units
45
46 506 will be informed of the timing of their treatment allocation (step) three months before
47
48 507 the active treatment is due to start. The treatment allocation will not be administered
49
50 508 blind and there are no restrictions on concomitant care or other interventions during
51
52 509 the study, hence there is no need for emergency unblinding and there are no
53
54 510 stopping rules for the study.
55
56
57 511

1
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3 512 **DATA COLLECTION**
4

5 513 For the main trial, data will be accessed from the information routinely collected
6
7 514 during the clinical management of the patient. For consistency, we will normally only
8
9 515 include data items which become available within four months after the delivery date
10
11 516 in question, although we may seek advice from the independently-chaired trial
12
13 517 steering committee (TSC) about exceptions as they arise. Different data sources will
14
15 518 be used for different regions of the study: (i) In Scotland the source data will be
16
17 519 SMR2 and the Scottish Birth record, (ii) In Ireland the source data will be the National
18
19 520 Perinatal Reporting System (NRPS http://www.esri.ie/health_information/nprs), (iii) In
20
21 521 Northern Ireland, the source data will be the Northern Ireland maternity Statistics
22
23 522 database (NIMATS), (iv) In England and Wales, the source data will be the ONS, or
24
25 523 other relevant body. Data will be collected retrospectively on an annual basis from all
26
27 524 sources. We will assume that data unavailable four months after the woman
28
29 525 delivered is likely to be unobtainable (but see note in Study Design section above).
30
31 526 Thus, data on the first year of the study will be collected at month 16; data on the
32
33 527 second year will be collected at month 28 etc.

34
35
36 528 Data are routinely collected. A formal request for data access will be made at the
37
38 529 start of the study. This will require (i) in Scotland – Privacy Advisory Committee
39
40 530 approval and a formal approach to NHS Scotland Information Services Division (ISD)
41
42 531 (ii) in Ireland a formal approach to NRPS (iii) NIMATS in Northern Ireland (iv) in
43
44 532 England and Wales a formal approach will be made to the relevant bodies.

45
46
47 533 Data will then be sent to the electronic Data Research and Innovation Service
48
49 534 (eDRIS) National Safe Haven (NHS National Services Scotland) by secure file
50
51 535 transfer protocol (or other similar) for storage and subsequent analysis within a
52
53 536 secure project area (dedicated to the AFFIRM study). Further information on the
54
55 537 National Safe Haven is available at [http://www.isdscotland.org/Products-and-](http://www.isdscotland.org/Products-and-Services/eDRIS/Becoming-an-eDRIS-User/#NSS-National-Safe-Haven)
56
57 538 [Services/eDRIS/Becoming-an-eDRIS-User/#NSS-National-Safe-Haven](http://www.isdscotland.org/Products-and-Services/eDRIS/Becoming-an-eDRIS-User/#NSS-National-Safe-Haven). Briefly, the
58
59
60

1
2
3 539 National Safe Haven is located on a secure server, in which trusted and authorised
4
5 540 researchers can analyse individual level data while maintaining the utmost
6
7 541 confidentiality. It is anticipated that all study analysis will be done within the Safe
8
9 542 Haven, using one of the available statistical packages (e.g. R, SPSS).

10
11 543 Identifiers on Scottish data within the National Safe Haven are concealed from
12
13 544 researchers. Data from outwith Scotland will be anonymised before submission to the
14
15 545 National Safe Haven. We propose that data submitted to the National Safe Haven
16
17 546 will be “anonymised” by the data provider. However, we propose that the
18
19 547 anonymisation link will be retained at the source so that it will be possible to re-link
20
21 548 data retrospectively. The rationale for retaining the ability of local data guardians to
22
23 549 re-link data is because it is important to retain the possibility of identifying individual
24
25 550 patients retrospectively. Examples include: (i) It is possible that some additional
26
27 551 important data may be available at a late stage on individual participants – e.g. in the
28
29 552 scenario where the woman or baby had a major adverse event and spent a long time
30
31 553 in hospital before discharge or death and (ii) Although our protocol and outcome
32
33 554 analysis does not require identifiable data, we believe this will be a ‘once in a lifetime’
34
35 555 study, and that subsequent secondary analyses could yield important information for
36
37 556 patients and for policy makers. If retrospective identification is not possible, this will
38
39 557 limit further analysis. One likely example of future analyses is to determine the effect
40
41 558 of the intervention on different causes of stillbirth. This is outwith the scope of the
42
43 559 current protocol, but could be done relatively straightforwardly, by linking nationally
44
45 560 recorded information on “cause” of stillbirth to our study database. We anticipate that
46
47 561 such additional analyses would require additional ethics approval, but without a
48
49 562 process by which to re-link data, it will not be possible to perform such subsequent
50
51 563 analyses.

52
53
54 564 All Investigators and study site staff involved with this study will comply with the
55
56 565 requirements of the Data Protection Act 1998 (or equivalent for those outwith the UK)

1
2
3 566 with regard to the collection, storage, processing and disclosure of personal
4
5 567 information and will uphold the Act's core principles. Published results will not contain
6
7 568 any personal data that could allow identification of an individual participant.
8

9
10 569 In addition to the data recorded above, all sites will be asked to provide a copy of
11
12 570 their guidelines around (i) maternal awareness of RFM and (ii) management of
13
14 571 women presenting with RFM. Copies of guidelines will be sought by the study office
15
16 572 (a) at the start of the study (b) immediately before initiation of the intervention in each
17
18 573 specific unit and (c) six months after initiation of the intervention in each specific unit.
19

20 574 For the nested qualitative study, we will perform interviews of healthcare workers and
21
22 575 a small nested cohort of pregnant women about their experiences of fetal movement
23
24 576 and of this intervention. We shall ensure a diversity of age and include nulliparous
25
26 577 and multiparous women (n=30 in total). Ten interviews will be conducted with each of
27
28 578 the following groups of health care providers: obstetricians, midwives and
29
30 579 sonographers/radiologists. The interviews will take a semi-structured format
31
32 580 (sensitising and piloting interviews will be conducted prior to the commencement of
33
34 581 the trial and in the first month of the nested qualitative study). This format will ensure
35
36 582 the same categories of data will be obtained from each participant but also allow
37
38 583 individual responses to be fully explored.
39

40
41 584

42 43 585 **STATISTICS AND DATA ANALYSIS**

44 45 586 *Sample size calculation*

46
47
48 587 The sample size is the number of women delivering in hospitals participating in the
49
50 588 study. This was initially planned to include sites in Scotland, totalling around 58,000
51
52 589 deliveries per year with 16 consultant led maternity units, 20 smaller units each
53
54 590 delivering less than 350 babies per year, and seven units delivering less than five
55
56 591 births per year. The units involved in Perinatal Ireland (an all-Ireland research
57
58
59
60

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2
3 592 consortium across 7 academic sites in Ireland currently funded by the Health
4
5 593 Research Board, Ireland) have 50,000 births per year with seven large sites.
6
7 594 Combining one or two of the smaller units and one larger unit into a single “hospital
8
9 595 group” for each local area could provide 24 hospital “groups” – the details of hospital
10
11 596 groupings will be reviewed and finalised immediately prior to randomisation. In total,
12
13 597 36 sites expressed interested in participating in the study, although 2 were unable to
14
15 598 participate in the study and withdrew before randomisation. In total, 34 units were
16
17 599 randomised, these were situated throughout the UK and Ireland (10 in England, 4 in
18
19 600 Ireland, 15 in Scotland and 5 in Wales) with 143,140 births per annum.

20
21 601 We calculated statistical power using the methodology for stepped wedge designs
22
23 602 proposed in Hussey and Hughes (2007).⁴² First, we analysed stillbirth event data
24
25 603 from the Scottish Perinatal and Infant Mortality and Morbidity Report (SPIMMR)
26
27 604 covering years 2005-2010 ¹⁷ to determine estimates of between- and within-unit
28
29 605 variability in stillbirth rate. Analysis was by generalized linear mixed model for binary
30
31 606 outcomes. The power calculation, as per equations (#7) and (#8) in ⁴² assumed:
32
33 607 significance level 5%; analysis by generalized linear mixed model; deliveries equally
34
35 608 distributed across hospital groupings; baseline stillbirth rate 0.438% ¹⁷; between-
36
37 609 cluster variance 0.00816.

38
39
40 610 Finally, the statistical power depends on the number of groups in which the
41
42 611 intervention is implemented at each stage of the stepped wedge design and the
43
44 612 duration of recruitment at each “step”. Our study design proposes sequential
45
46 613 introduction of the intervention into three hospital groups at a time at four month
47
48 614 intervals over a 32 month period. It is anticipated that unavailability of data and
49
50 615 women asking to withdraw their data will be less than 1%. This would give 89.9%
51
52 616 power to detect a 30% risk reduction under the intervention and 77.0% power to
53
54 617 detect a 25% reduction. A 30% risk reduction was seen in the Norwegian study; the
55
56 618 anticipated effect sizes of 25% and 30% relative reduction take into account that the
57
58
59
60

1
2
3 619 intervention will not have the power to reduce all stillbirths, since 20% of stillbirths in
4
5 620 Ireland⁴³ and 15% in Scotland¹⁷ are associated with congenital anomaly.

6
7 621 *Proposed analyses*

8
9
10 622 For the binary primary and secondary outcomes, data will be analysed by
11
12 623 generalized linear mixed model with a random effect for hospital and fixed effects for
13
14 624 the intervention implementation and study time period. A site by intervention
15
16 625 interaction random effect will be included in the model and retained if it explains an
17
18 626 important proportion of the variability in outcomes. The primary analysis of data will
19
20 627 be on an intention to treat basis (the design of the trial means it is not possible to
21
22 628 determine individual patient /caregiver compliance with the intervention). An “on
23
24 629 treatment” variable will be calculated for which women will be grouped as active or
25
26 630 control according to when the intervention was actually implemented in their site,
27
28 631 instead of when the site was randomised to implement the intervention. The primary
29
30 632 outcome will be reanalysed in two sensitivity analyses. Firstly, we will perform the
31
32 633 analysis according to the actual timing of the implementation of the intervention
33
34 634 rather than the randomised timing of the intervention using the “on treatment”
35
36 635 classification. Secondly, we will perform the analysis in the subgroup of sites who
37
38 636 were deemed to have implemented the intervention effectively according to the
39
40 637 perception of the Principal Investigator at each site. The accuracy of this perception
41
42 638 will be confirmed with the findings of a site audit (details in Supplementary
43
44 639 Information 2). There will be no attempt to correlate the impact of the intervention
45
46 640 according to the results of the site audit.

47
48
49 641 There are no planned imputations for missing data. However, if the missing data rate
50
51 642 for smoking status during pregnancy is relatively high an imputation technique will be
52
53 643 devised. The imputation method will be informed using smoking history at booking
54
55 644 and age at delivery⁴⁴. A pre-specified subgroup analysis will be performed for babies
56
57 645 with and without congenital anomalies, and will be implemented by testing for an

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3 646 intervention by congenital anomaly interaction added to the generalised linear mixed
4
5 647 model described above. No formal interim analyses for efficacy or safety will be
6
7 648 performed. A full statistical analysis plan will be finalised prior to locking of the study
8
9 649 database.

10
11 650 *Qualitative Data*

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13
14 651 For the nested qualitative study, the data will be audio recorded and transcribed.
15
16 652 The data will be coded thematically and an analytical framework developed to make
17
18 653 sense of patient experience of fetal movement and the intervention and also health
19
20 654 care providers' perspectives and experiences. NVivo will be utilised to support the
21
22 655 analysis.

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24
25 656 *Process outcomes*

26
27 657 The process outcomes being assessed by the (rates of induction of labour, number
28
29 658 of women presenting with reduced fetal movements, interval between perceiving fetal
30
31 659 movements and presenting to hospital) will be analysed using the same methods as
32
33 660 for the main trial, with the exception of the continuous outcome (interval between
34
35 661 perceiving fetal movements and presenting to hospital) which will be analysed using
36
37 662 a normal linear mixed model.

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40 663 **ADVERSE EVENTS**

41
42 664 This is not a Clinical Trial of an Investigational Medicinal Product (CTIMP) so adverse
43
44 665 events will not be formally reported. Stillbirth and other measures of fetal and
45
46 666 maternal morbidity are outcomes of the study. The purpose of the intervention is to
47
48 667 reduce such adverse events. Therefore, due to the low risks for this trial, a separate
49
50 668 DMC is not required and the Trial Steering Committee (TSC) will cover any
51
52 669 responsibilities normally allocated to a DMC. If considered necessary, the TSC may
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54 670 review unblinded data for the study, including morbidity and mortality indices. No
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56 671 other adverse event reporting will be undertaken.
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For peer review only

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673 TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

674 The trial will be coordinated by a Project Management Group, consisting of the grant
675 holders and the Trial Manager. The Chief Investigator (JN) will lead the project
676 management group. The Trial Manager will oversee the study and will be
677 accountable to the Chief Investigator. A TSC will be established to oversee the
678 conduct and progress of the trial. The terms of reference and a draft template for
679 reporting will be ratified in one of the early meetings of the TSC.

680 Investigators and institutions involved in the study will permit trial related monitoring
681 and audits on behalf of the co-sponsors (ACCORD: Academic and Clinical Central
682 Office for Research & Development - Joint office for University of Edinburgh and
683 NHS Lothian, Sponsor contact: ray.french@ed.ac.uk), research ethics committee
684 (REC) review, and regulatory inspection(s). In the event of an audit or monitoring, the
685 Investigator agrees to allow the representatives of the sponsor direct access to all
686 study records and source documentation. In the event of regulatory inspection, the
687 Investigator agrees to allow inspectors direct access to all study records and source
688 documentation.

689

690 *Study monitoring and audit*

691 The sponsor determined that as no individual participants were recruited to the
692 intervention, and it was not a clinical trial of an investigational medicinal product
693 (CTIMP) no formal monitoring and audit was required.

694

695 *Good Clinical Practice and Ethical Conduct*

696 The study will be conducted in accordance with the principles of the research
697 governance framework operational and good clinical practice in the relevant country.
698 A favorable ethical opinion has been obtained from the Scotland A REC (Reference

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2
3 699 13/SS/0001) and local research and development approval has been obtained prior
4
5 700 to commencement of the study.
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7
8 701 Local study investigator(s) will be appointed to each site (or for small units, groups of
9
10 702 sites). S/he will be responsible for the overall conduct of the study at the site and
11
12 703 compliance with the protocol and any protocol amendments.
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16 17 705 **STUDY CONDUCT RESPONSIBILITIES**

18 19 706 *Protocol amendments*

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21
22 707 Any changes in research activity, except those necessary to remove an apparent,
23
24 708 immediate hazard to the participant in the case of an urgent safety measure, will be
25
26 709 reviewed and approved by the Chief Investigator and Sponsor. Amendments to the
27
28 710 protocol will be submitted in writing to the appropriate REC and local Research and
29
30 711 Development (R&D) department for approval prior to participants being enrolled into
31
32 712 an amended protocol.
33

34 35 713 *Protocol violations and deviations*

36
37 714 Investigators will not implement any deviation from the protocol without agreement
38
39 715 from the Chief Investigator and appropriate REC and R&D department approval
40
41 716 except where necessary to eliminate an immediate hazard to trial participants. In the
42
43 717 event that an Investigator needs to deviate from the protocol, the nature of and
44
45 718 reasons for the deviation will be recorded. If this necessitates a subsequent protocol
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47 719 amendment, this will be submitted to the REC, and local R&D department for review
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49 720 and approval if appropriate.
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51 52 721 *Serious breach requirements*

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54 722 A serious breach is one which is likely to effect to a significant degree (a) the safety
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56 723 or physical or mental integrity of the participants of the trial; or b) the scientific value
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3 724 of the trial. If a potential serious breach is identified by the Chief investigator,
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5 725 Principal Investigator or delegates, the co-sponsors
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7 726 (accord.seriousbreach@ed.ac.uk) will be notified within 24 hours. It will be the
8
9 727 responsibility of the co-sponsors to assess the impact of the breach on the scientific
10
11 728 value of the trial, to determine whether the incident constitutes a serious breach and,
12
13 729 if so, report it to the REC.

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15 730 All violations will be assessed by the sponsor(s) to ascertain if they meet the criteria
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17 731 for a serious breach. If the sponsor(s) deem the incident to be a violation that does
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19 732 not constitute a serious breach from the protocol when identified, corrective and
20
21 733 preventative actions will be taken where appropriate and they will be recorded in file
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23 734 notes, held within the TMF and ISF.

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26 735 *Study record retention*

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29 736 All study documentation will be kept for a minimum of 5 years from the protocol
30
31 737 defined end of study point. When the minimum retention period has elapsed, study
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33 738 documentation will not be destroyed without permission from the sponsor.

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38 740 *End of study*

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40 741 The end of study date was finalised in the protocol after the study commenced; the
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42 742 agreed end of study date is 31/12/2016. The Investigators and/or the trial steering
43
44 743 committee and/or the co-sponsor(s) have the right at any time to terminate the study
45
46 744 for clinical or administrative reasons.

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49 745 The end of the study will be reported to the REC within 90 days, or 15 days if the
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51 746 study is terminated prematurely. The Investigators will inform participants of the
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53 747 premature study closure and ensure that the appropriate follow up is arranged for all
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55 748 participants involved. A summary report of the study will be provided to the REC and
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57 749 Regulatory Authority within 1 year of the end of the study.
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5 751 **REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS**
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8 752 Ownership of the data arising from this study resides with the study team. On
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10 753 completion of the study, the study data will be analysed and tabulated, and a clinical
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12 754 study report will be prepared in accordance with good clinical practice guidelines.
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14 755 The clinical study report will be used as the basis for publication and presentation at
15
16 756 scientific meetings. Investigators have the right to publish orally or in writing the
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18 757 results of the study. Summaries of results will also be made available to Investigators
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20 758 for dissemination within their clinics (where appropriate and according to their
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22 759 discretion).
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27 761 **DISCUSSION**
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30 762 The data provided by this study will inform the information given to women about
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32 763 reduced fetal movements and their management when they present to maternity
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34 764 services; which has been recurrently identified by Confidential Enquiries into
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36 765 antepartum stillbirths as suboptimal^{27 28}. Data from the AFFIRM study will be able to
37
38 766 be compared to results from two other active studies which aim to improve mothers
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40 767 awareness and reporting of reduced fetal movements. My Babies Movement
41
42 768 (ACTRN 12614000291684) is stepped-wedge cluster trial of a mobile phone
43
44 769 application to help women get to know their baby's movements, to be mindful of
45
46 770 movements every day and not to wait to report concerns to their maternity care
47
48 771 provider. The Mindfetalness study (NCT02865759) is a cluster trial of 39,000 women
49
50 772 randomised to routine antenatal care or the Mindfetalness brochure and website.⁴⁵
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52 773 Women participating in the Mindfetalness process will spend 15 minutes each day
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54 774 getting to know their babies movements and will specifically be encouraged to
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56 775 contact their health provider if their perceive reduced fetal movements. This primary
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3 776 outcome of this study is an Apgar score <7 at 5 minutes; stillbirth and perinatal
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5 777 deaths will be recorded as tertiary endpoints of this study.⁴⁵ These large studies will
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7 778 provide much needed robust evidence to determine whether increased maternal
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9 779 awareness of reduced fetal movements combined with a standardised management
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11 780 protocol to identify acute or chronic fetal compromise can reduce stillbirth³³.

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16 782 **PEER REVIEW**

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18 783 This project has been peer reviewed internally, and was externally peer reviewed
19
20 784 during the process of securing funding from the Chief Scientist's Office of the
21
22 785 Scottish Government, Tommy's and Sands.

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27 787 **FUNDING**

28
29 788 The AFFIRM study is investigator initiated and funded by Chief Scientist Office,
30
31 789 Scottish Government (CZH/4/882), Tommy's and Sands, the Stillbirth and Neonatal
32
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34
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36
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38
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40
41 794 The views expressed are those of the author(s) and not necessarily those of the
42
43 795 NHS, the NIHR or the Department of Health.

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48
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50
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56 801 **CONTRIBUTIONS**

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2
3 802 Contributors AEPH, CJW, SJES, CJC, SCB, MRD, SW and JEN were involved in
4
5 803 developing the trial design. AEPH, CJW, SJES, AR and JEN were involved in
6
7 804 drafting and revision of the article. CJW and AR were involved in drafting the
8
9 805 statistical aspects of the protocol. JS provided feedback on behalf of a stakeholder
10
11 806 organisation. AEPH, CJW, SJES, CJC, SCB, JFF, MG, AH, FMM, EM, AR, MRD, JS,
12
13 807 SW and JEN were involved in preparing the overall study design. AEPH, JEN and
14
15 808 MRD prepared education videos for online training. AEPH, SJES, SJS, MG, AH,
16
17 809 FMM and JEN facilitated recruitment of sites. AEPH, CJW, SJES, CJC, SCB, JFF,
18
19 810 MG, AH, FMM, EM, AR, MRD, JS, SW and JEN will be involved in the collection,
20
21 811 management, analysis and interpretation of data and final writing of the trial report.
22

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25 813 **COMPETING INTERESTS**

26
27 814 None declared.
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815 **ABBREVIATIONS**

816	ACCORD	Academic and Clinical Central Office for Research & Development -
817		Joint office for University of Edinburgh and NHS Lothian
818	BMI	Body Mass Index
819	CTG	Cardiotocograph
820	CTIMP	Clinical Trial of an Investigational Medicinal Product
821	ECTU	Edinburgh Clinical Trials Unit
822	FGR	Fetal growth restriction
823	MHRA	Medicines and Healthcare products Regulatory Agency
824	NICE	National Institute for Health and Social Care Excellence
825	NIHR	National Institute for Health Research
826	NIMATS	Northern Ireland Maternity Statistics database
827	NRPS	National Perinatal Reporting System
828	ONS	Office of National Statistics
829	PSANZ	Perinatal Society of Australia and New Zealand
830	RCOG	Royal College of Obstetricians and Gynaecologists
831	R&D	Research and Development
832	REC	Research Ethics Committee
833	RFM	Reduced Fetal Movements
834	SPIMMR	Scottish Perinatal and Infant Mortality and Morbidity Report
835	TMF	Trial Master File
836	TSC	Trial Steering Committee
837	WHO	World Health Organisation
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839		

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977 mindfetalness. *Sexual & reproductive healthcare : official journal of the*
978 *Swedish Association of Midwives* 2016;10:56-61.
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3 982 **FIGURE LEGENDS**
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5 983 Figure 1 - Stepped wedge design. The shaded areas (both light and dark) indicate
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7 984 periods in which the interventions are being implemented. The lighter areas indicate
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9 985 the “transition” period during which data will not be collected for the control or
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11 986 intervention group. The order in which hospital groupings implement the interventions
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13 987 will be determined via randomization.
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16 988 Figure 2 – Flow chart for the management of women presenting with reduced fetal
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18 989 movements for sites implementing the AFFIRM study. Abbreviations: AC - abdominal
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20 990 circumference, CTG- cardiotocograph, DVP - deepest vertical pool, EFW - estimated
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22 991 fetal weight, FGR - fetal growth restriction, LV - liquor volume, RFM - reduced fetal
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24 992 movement, USS - ultrasound scan.
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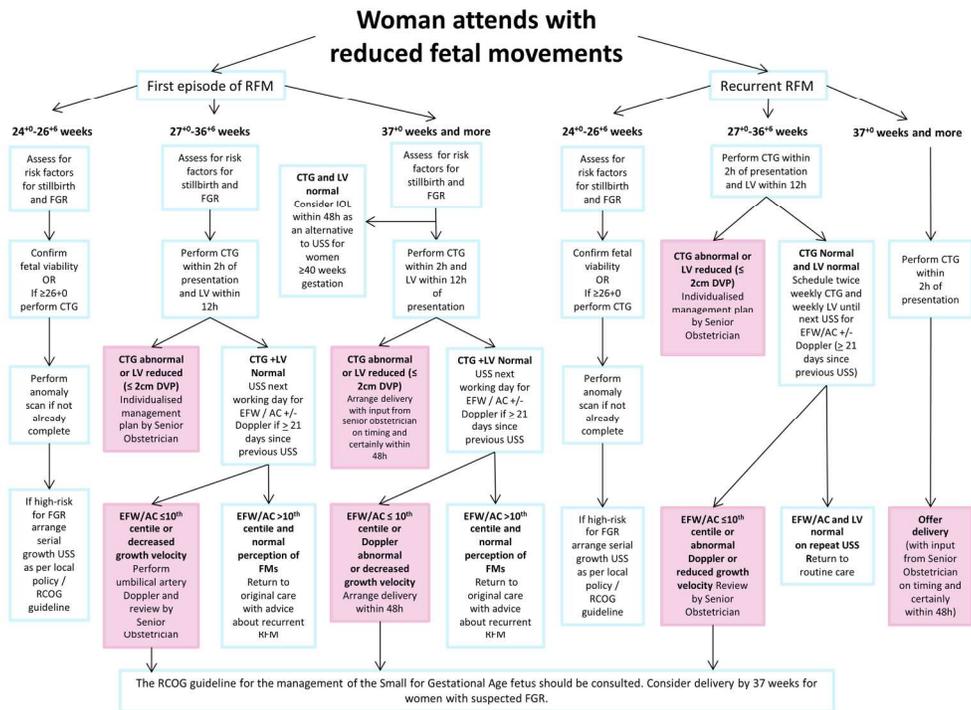
Hospital groupings	Months since Start of Trial								
	1-4	5-8	9-12	13-16	17-20	21-24	25-28	29-32	33-36
1-3		Light	Dark						
4-6			Light	Dark	Dark	Dark	Dark	Dark	Dark
7-9				Light	Dark	Dark	Dark	Dark	Dark
10-12					Light	Dark	Dark	Dark	Dark
13-15						Light	Dark	Dark	Dark
16-18							Light	Dark	Dark
19-21								Light	Dark
22-24									Light

Stepped wedge design. The shaded areas (both light and dark) indicate periods in which the interventions are being implemented. The lighter areas indicate the "transition" period during which data will not be collected for the control or intervention group. The order in which hospital groupings implement the interventions will be determined via randomization.

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Flow chart for the management of women presenting with reduced fetal movements for sites implementing the AFFIRM study. Abbreviations: AC - abdominal circumference, CTG- cardiotocograph, DVP - deepest vertical pool, EFW - estimated fetal weight, FGR - fetal growth restriction, LV - liquor volume, RFM - reduced fetal movement, USS - ultrasound scan.

190x142mm (300 x 300 DPI)

WHO TO CONTACT IF YOU ARE CONCERNED: (space for sticky with local contact information)



APS Group Scotland
DPPAS33137
Version 3 March 2015



In touch with **YOUR BABY**

A guide to your baby's
movements during
pregnancy



For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

Why are my baby's movements important?

Why are we asking women to get to know their baby's movements?

One of the easiest ways to tell if your baby is healthy is to be aware of how much he or she is moving. Every baby is different and we are asking women to take time to become familiar with their baby's own individual pattern of movements. A reduction or change in **your** baby's movements is what is important.

What can affect my baby's movements?

You are less likely to be aware of your baby's movements when active or busy. Some drugs e.g. strong pain relief or sedatives can get into an unborn baby's circulation and affect the movements. Alcohol and smoking (active and passive smoking) may also affect the baby.

Why are my baby's movements important?

If you notice your baby is moving less than usual, or the pattern of movements has changed, this could be the first sign that your baby may not be well or is not growing properly in the womb. Research has shown that a reduction in the baby's movements may indicate an increased risk of stillbirth. You may hear your midwife or doctor referring to 'reduced fetal movement', or RFM for short.

What are the risks of stillbirth?

Stillbirth affects one in 200 babies after 24 weeks gestation and is one of the most common of the serious complications of pregnancy, affecting the lives of around 4,000 families every year in the UK.

One of the easiest ways to tell if your baby is healthy is to see how much he or she is moving. This booklet tells you what to look out for during your pregnancy.



Every baby is different. It is good to get to know your baby's own movements and the pattern of their sleeping and waking and report to us if you notice a reduction in these movements.

Try to get to know the times of the day when you are most likely to feel your baby move.



18-24 WEEKS



24-36 WEEKS



Most women begin to feel their baby move between 18-24 weeks. At first it may feel like 'bubbles', 'flutterings' or 'like trapped wind'. These are often very short and stop and start. It might take you a little while to be sure what you are feeling. But you will soon get to know the feelings. If this is your second baby, you will know what to look out for and may recognise your baby moving sooner.

Everyone is different when it comes to their movements. There are many reasons you might not feel movements as early as you expect. This includes your body weight, the position of your baby and the location of your placenta. What is important is your baby is growing well. Your midwife will be able to discuss this with you further at your 22 week check.

You will have your own way of describing your baby's own movements. Women often describe their baby's movements as 'rolling', 'kicking', 'pushing', 'jabs', 'elbowing' and 'stretches'.

Between 24-36 weeks you will start to recognise your baby's movements more quickly and become more used to the feeling. It is usually easier to feel your baby's movements when you are lying down, e.g. at night time. It is harder to feel your baby move when you are on your feet and moving around.

Try to get to know the times of the day you are most likely to feel your baby move. This will help you to know if he or she is moving less than normal or if movements have stopped.

Occasionally your baby will get hiccups. These do not count as movements. If you are unsure what you should expect when your baby hiccups, speak to your midwife.



Appendix 3 - Audit of compliance with AFFIRM protocol

Compliance with the AFFIRM management protocol (the management plan for women presenting with reduced fetal movement) will be determined by to means:

A) Telephone / email contact with Principal Investigators at each site to determine which aspects of the AFFIRM protocol have been implemented effectively.

This will involve email contact with Principal Investigators to alert them to the request for information, an email detailing the information required, and then a phone call to elicit the information (unless it had already been supplied). Investigators will be asked which of the following elements they had implemented: issuing leaflets to all pregnant women, cardiotocography within 2 hours of presentation, measurement of amniotic fluid volume within 12 hours of presentation, growth scan by the next working day for all women presenting with reduced fetal movement (and who had not had a growth scan within the last three weeks, or who were not being induced within 48 hours), and induction of labour within 48 hours for women presenting with recurrent reduced fetal movement at or after 37 weeks gestation. "Effective implementation" was defined as the above management for 4/5 of these elements for 80% or more of the time.

B) An audit to determine whether the perception of the site Principal Investigator is supported by review of actual decision making will be performed for the following elements: cardiotocography within 2 hours of presentation, measurement of amniotic fluid volume within 12 hours of presentation, growth scan by the next working day for all women presenting with reduced fetal movement (and who had not had a growth scan within the last three weeks, or who were not being induced within 48 hours), and induction of labour within 48 hours for women presenting with recurrent reduced fetal movement at or after 37 weeks gestation.

This will be conducted by asking sites to complete an audit of the management of all women presenting with reduced fetal movement over the course of one calendar month. Sites will be asked to complete an audit form for each participant. The audit form template (see below) has been generated by the central

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2 AFFIRM study team; anonymized forms will be analysed centrally. There will not be an attempt to corroborate Principal Investigator perception of the
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4 proportion of women who were given leaflets, nor will there be any attempt to incorporate the proportion of staff who had completed the e-learning
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6 package into analysis of whether any specific site has implemented the intervention or not.
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Compliance with AFFIRM reduced fetal movements protocol, One month data collection AUDIT [Month & Year] Unit name: [Name of Hospital]

If you assess a woman with reduced fetal movements (RFM), please complete the questions below. Do not worry if the woman has been seen in other areas of the hospital by other staff, we would rather have multiple reports for the same woman than miss episodes of RFM.

INSERT Patient Sticker (or WRITE name and CHI /NHS number)				AREA WHERE SEEN (CIRCLE) Triage / Labour ward / Day Assessment Unit (DAU) Other (specify area i.e. antenatal ward): _____							
Date and time of presentation with reduced fetal movements.	DATE: ____/____/____ TIME ____:____ am / pm			GESTATION AND EDD:	_____ WEEKS _____ DAYS EDD: _____						
Referred by (TICK BOX):	<input type="checkbox"/> Self	<input type="checkbox"/> Community Midwife	<input type="checkbox"/> GP	<input type="checkbox"/> ANC	<input type="checkbox"/> Triage	<input type="checkbox"/> DAU	<input type="checkbox"/> Other (specify: _____)				
What was the primary reason for attending/phoning? (TICK BOX):	<input type="checkbox"/> Reduced Fetal Movements			<input type="checkbox"/> Other (specify: _____)							
How many times has the woman attended before this visit, with RFM? (TICK BOX):	<input type="checkbox"/> None – first attendance		<input type="checkbox"/> Once previously		<input type="checkbox"/> Unknown	<input type="checkbox"/> Multiple times (please provide the gestation at each presentation i.e. 30+6)	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
What was the time interval from the woman first being aware of reduced fetal movements and attending the hospital (in hours)?						HOURS: _____					
Has she been given a leaflet "Your baby's movements in pregnancy"? (TICK BOX):	<input type="checkbox"/> Yes – she already has one		<input type="checkbox"/> Yes – I have given one to her today			<input type="checkbox"/> Locally Created Leaflet Given	<input type="checkbox"/> NO				
Has this woman had a growth USS in this pregnancy? (TICK BOX):	<input type="checkbox"/> No, she has not had a growth scan		<input type="checkbox"/> Yes, within the last 3 weeks (date of scan): DATE: ____/____/____			<input type="checkbox"/> Yes, but more than 3 weeks ago (date of scan): DATE: ____/____/____					

CONTINUATION: NHS/ CHI NUMBER:

Are any of the following risk factors for Fetal growth restriction present (CIRCLE all that apply)?							
Age ≥40 or ≤16	Smoker ≥20cpd	Known or suspected growth restriction	Congenital anomaly	Raised BP (essential hypertension, pre-eclampsia or pregnancy induced hypertension)	Previous pre-eclampsia	Diabetes or gestational diabetes	Previous FGR or stillbirth
What investigations were conducted during this episode of reduced fetal movement?							
Please record below the date and time that these investigations were completed or indicate if not performed.						Please provide the results (CIRCLE):	
CTG	Not performed	<input type="checkbox"/>	DATE: __/__/____	TIME: ____:____ am/pm	Normal / Suspicious / Pathological		
Computerised CTG: YES / NO (CIRCLE)							
Liquor volume assessment on scan	Not performed	<input type="checkbox"/>	DATE: __/__/____	TIME: ____:____ am/pm	Normal / Reduced / Increased		
Growth scan	Not performed	<input type="checkbox"/>	DATE: __/__/____	TIME: ____:____ am/pm	Normal / EFW < 10 th centile/ AC < 10 th centile / EFW and AC < 10 th centile		
Umbilical Artery Doppler	Not performed	<input type="checkbox"/>	DATE: __/__/____	TIME: ____:____ am/pm	Normal/.> 95 th centile/absent EDF/reversed EDF		
MCA Doppler	Not performed	<input type="checkbox"/>	DATE: __/__/____	TIME: ____:____ am/pm	Normal/<5 th centile		
DELIVERY METHOD (If available)							
Was the woman offered induction of labour	YES / NO (CIRCLE) IF Yes, please provide date, time and method of the induction:			DATE: ____/____/____ TIME: ____:____ am/pm			
Was the woman offered elective caesarean section as a result of the reduced fetal movement?	YES / NO (CIRCLE) IF Yes, please provide date, time and reason:			DATE: ____/____/____ TIME: ____:____ am/pm		Please provide the reason for the elective Caesarean section:	



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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___ Page 1 ___
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___ Page 4 ___
	2b	All items from the World Health Organization Trial Registration Data Set	_Included throughout protocol_
Protocol version	3	Date and version identifier	___ Page 4 ___
Funding	4	Sources and types of financial, material, and other support	___ Page 28 ___
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_Names and affiliations Page 1 and 2; Contributions Page 28_
	5b	Name and contact information for the trial sponsor	___ Page 24 ___
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_Not applicable_

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3		5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
4			___Page 24___
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8	Introduction		
9			
10	Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
11			__Pages 5-11__
12		6b	Explanation for choice of comparators
13			__Pages 8-9__
14	Objectives	7	Specific objectives or hypotheses
15			__Pages 11-12__
16	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
17			__Pages 13- 14 and Figure 1__
18			
19			
20	Methods: Participants, interventions, and outcomes		
21			
22	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
23			__Pages 13 & 16__
24			
25	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
26			__Pages 14-15__
27			
28	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
29			__Pages 17-18 and Figure 2__
30		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
31			__Not applicable in AFFIRM trial__
32		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
33			__Pages 17-18__
34		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
35			__Not applicable__
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3	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	__Pages 12-13__
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8	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	__Randomisation by site explained in Figure 1 and Pages 13-14__
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14	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	__Pages 21-22__
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17	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	__Page 22__
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20	Methods: Assignment of interventions (for controlled trials)			
21	Allocation:			
22				
23	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	__Page 17__
24				
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29	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	__Page 17__
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33	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	__Page 17__
34				
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36	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	__Page 17__
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39		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_ Not applicable in AFFIRM study__
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3 **Methods: Data collection, management, and analysis**
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5 Data collection	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	__Pages 18-21__
6 methods			
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	__Not applicable__
14 Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	__Pages 19-20__
18 Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	__Pages 22-23__
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	__Page 23__
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	__Pages 22-23__

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27 **Methods: Monitoring**
28

29 Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_DMC not required, explanation Pg 24__
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	__Pages 18, 25-26__
37 Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	__Page 24__
41 Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	__Page 13__

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Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	__Page 25__
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	__Page 25__
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	__Page 25__
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	__Not applicable__
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	__Page 20__
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	__Page 29__
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	__Page 27__
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	__Page 24__
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	__Page 27__
	31b	Authorship eligibility guidelines and any intended use of professional writers	__Page 28__
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	__Not applicable__

Appendices

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2				
3	Informed consent	32	Model consent form and other related documentation given to participants and authorised surrogates	_Not Applicable_
4	materials			
5				
6	Biological	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular	_Not Applicable_
7	specimens		analysis in the current trial and for future use in ancillary studies, if applicable	
8				

9 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
10 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
11 "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.
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BMJ Open

Can Promoting Awareness of Fetal movements and Focussing Interventions Reduce Fetal Mortality? - A stepped wedge cluster randomised trial (AFFIRM)

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-014813.R2
Article Type:	Protocol
Date Submitted by the Author:	07-Feb-2017
Complete List of Authors:	<p>Heazell, Alexander; University of Manchester, Maternal and Fetal Health Research Centre Weir, Christopher; University of Edinburgh, MRC Hub for Trials Methodology Research; Edinburgh Clinical Trials Unit Stock, Sarah; Queen's Medical Research Institute, EH16 4TJ, Tommy's Centre for Maternal and Fetal Health, MRC Centre for Reproductive Health,; School of Women's and Infants' Health, University of Western Australia, Crawley WA 6009. (FMM) Calderwood, Catherine; The Scottish Government St Andrew's House, EH1 3DG., Chief Medical Officer for Scotland, CunninghamBurley, Sarah; University of Edinburgh, Public Health Sciences Froen, Frederik; Nasjonalt folkehelseinstitutt, Division of Epidemiology Geary, Michael; Rotunda Hospital, Parnell Square Hunter, Alyson; Royal Maternity Hospital, Grosvenor Road, BT12 6BB McAuliffe, Fionnuala; University College Dublin, Murdoch, Edile; Royal Infirmary of Edinburgh, NHS Lothian, EH16 4SA., Department of Neonatology Rodriguez, Aryelly; University of Edinburgh, (ECTU) Edinburgh Clinical Trials Unit Ross-Davie, Mary; NHS Education for Scotland, 3rd Floor, Hanover Buildings, 66 Rose Street, EH2 2NN. Scott, Janet; Sands, Victoria Charity Centre, Suite GF2 Ground Floor, 11 Belgrave Road, SW1V 1RB. Whyte, Sonia; Queen's Medical Research Institute, EH16 4TJ, Tommy's Centre for Maternal and Fetal Health, MRC Centre for Reproductive Health, Norman, Jane; , Queen's Medical Research Institute, EH16 4TJ</p>
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Research methods
Keywords:	Reduced Fetal Movements, Perinatal Mortality, Stillbirth, Neonatal Death, Fetal Growth Restriction

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3 **1 Study Protocol**
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5 2 Can Promoting Awareness of Fetal movements and Focussing Interventions Reduce
6 3 Fetal Mortality? - A stepped wedge cluster randomised trial (AFFIRM)
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1
2
3 40 **Abstract**
4

5 41 *Background* - In 2013, the stillbirth rate in the UK was 4.2 per 1,000 live births,
6
7 42 ranking 24th out of 49 high-income countries, with an annual rate of reduction of only
8
9 43 1.4% per year. The majority of stillbirths occur in normally formed infants, with
10
11 44 (retrospective) evidence of placental insufficiency the commonest clinical finding.
12
13 45 Maternal perception of reduced fetal movements (RFM) is associated with placental
14
15 46 insufficiency and increased risk of subsequent stillbirth.

17
18 47 This study will test the hypothesis that the introduction of a package of care to
19
20 48 increase women's awareness of the need for prompt reporting of RFM and
21
22 49 standardised management to identify fetal compromise with timely delivery in
23
24 50 confirmed cases, will reduce the rate of stillbirth. Following the introduction of a
25
26 51 similar intervention in Norway the odds of stillbirth fell by 30%, but the efficacy of this
27
28 52 intervention (and possible adverse effects and implications for service delivery) have
29
30 53 not been tested in a randomised trial.

31
32
33 54 *Methods* - We describe a stepped wedge cluster trial design, in which participating
34
35 55 hospitals in the UK and Ireland will be randomized to the timing of introduction of the
36
37 56 care package. Outcomes (including the primary outcome of stillbirth) will be derived
38
39 57 from detailed routinely collected maternity data, allowing us to robustly test our
40
41 58 hypothesis. The degree of implementation of the intervention will be assessed in
42
43 59 each site. A nested qualitative study will examine the acceptability of the intervention
44
45 60 to women and health care providers and identify process issues including barriers to
46
47 61 implementation.

48
49 62 *Discussion* - The data provided by this study will inform the management of women
50
51 63 with RFM; which has been recurrently identified as suboptimal in cases of stillbirth.
52
53 64 This will provide robust evidence to determine whether increased maternal
54
55 65 awareness of RFM combined with a standardised management protocol to identify
56
57 66 acute or chronic fetal compromise can reduce stillbirth.
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3 67 *Trial Registration*

4
5 68 www.clinicaltrials.gov NCT01777022

6
7
8 69 *Version*

9
10 70 Protocol Version 4.2, 19th December 2016

11
12 71 *Keywords*

13
14
15 72 Reduced Fetal Movements; Perinatal Mortality; Stillbirth; Neonatal Death; Fetal
16
17 73 Growth Restriction.

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19
20 74

21
22 75 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

23
24 76 • This trial directly addresses the need for studies of the information given to
25
26 77 women regarding fetal movements and the subsequent management of reduced
27
28 78 fetal movements identified by Confidential Enquiries into Antepartum Stillbirths,
29
30 79 Systematic Reviews and the Stillbirth Priority Setting Partnership.

31
32 80 • A stepped-wedge cluster trial design in combination with routinely collected
33
34 81 maternity data allows the trial to be adequately powered to detect a difference in
35
36 82 stillbirth as a primary outcome.

37
38 83 • The pragmatic nature of the study represents the potential impact of the
39
40 84 introduction of such standardised care into clinical practice.

41
42 85 • The nested qualitative study will provide information regarding the acceptability
43
44 86 of the intervention and identify barriers and facilitators to its adoption.

45
46 87 • The lack of information on resource use before and throughout the study period
47
48 88 limits the ability to understand the consequences of the intervention on maternity
49
50 89 unit workload.

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1
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3 92 **INTRODUCTION**
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5 93 *Stillbirth*
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7
8 94 Stillbirth, defined in the UK as a baby with no signs of life after 24 weeks of completed
9
10 95 pregnancy ¹, remains the major cause of perinatal mortality in high-income
11
12 96 environments, with a recent series of papers in the Lancet on stillbirth issue calling for
13
14 97 renewed action in this area ². There is no single “cause” of stillbirth, and a significant
15
16 98 proportion of stillbirths remain unexplained, but fetal growth restriction, maternal
17
18 99 hypertension and low socioeconomic status are amongst the identifiable risk factors ³.
19
20 100 The concept that more can be done to reduce stillbirth in the UK and Ireland is
21
22 101 supported by data showing a marked variation in rates between resource rich
23
24 102 countries, when similar definitions of stillbirth are used ². Notably, the UK has a higher
25
26 103 rate than comparable resource rich countries such as Germany, Netherlands, New
27
28 104 Zealand and Norway with rates in the UK some 50% greater than those of the
29
30 105 Netherlands. Disappointingly, the annual rate of reduction in stillbirth from 2000 to
31
32 106 2014 in the UK was only 1.4% compared to 6.8% in the Netherlands and 2.8% in New
33
34 107 Zealand ². Rates of stillbirth in Scotland (3.7 per 1,000 births in 2014) and Ireland, at
35
36 108 (4.4 per 1,000 livebirths in 2013) are similar to rates in England and Wales at 4.2 per
37
38 109 1,000 livebirths (England and Wales, 2014) ⁴. The reduction of avoidable harm for
39
40 110 women and babies is viewed as a major priority for Government and its agencies
41
42 111 throughout the UK and Ireland. Consequently, several initiatives have been
43
44 112 developed by national governments in the UK and Ireland including the Scottish
45
46 113 Government Stillbirth Working Group, NHS England Saving Babies’ Lives Care
47
48 114 Bundle and the Welsh Assembly 1000 Lives Plus strategy. These strategies have
49
50 115 identified the need for better evidence to guide efforts to prevent stillbirths.
51
52
53 116 Using a robust priority setting strategy ⁵ the Lancet Stillbirth’s series steering
54
55 117 committee identified issues around detection and management of reduced fetal
56
57 118 movements (RFM) amongst the top ten key research questions on prevention and
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3 119 management of stillbirth⁶. This was confirmed in the UK-based Stillbirth Priority
4
5 120 Setting partnership involving over 1,700 parents and professionals which identified
6
7 121 two relevant issues among the highest ranked research questions regarding stillbirth:
8
9 122 i) which investigations identify a fetus at risk of stillbirth after a mother believes she
10
11 123 has experienced reduced fetal movements? and ii) would more accessible evidence-
12
13 124 based information on signs and symptoms of stillbirth risk, designed to empower
14
15 125 women to raise concerns with healthcare professionals, reduce the incidence of
16
17 126 stillbirth?⁷ Thus, RFM has been identified as a highly-relevant area of study by
18
19 127 parents, professionals and researchers.
20
21 128

22 23 129 *Reduced Fetal Movements, Stillbirth and Placental Insufficiency*

24
25
26 130 There is a clear association between maternal perception of RFM and late stillbirth
27
28 131 dating back over four decades⁸. In a recent series of 2,000 women, the adjusted OR
29
30 132 (95% CI) of late stillbirth in women with RFM (compared with controls) was 2.37
31
32 133 (1.29-4.35)⁹. One international study of 1,714 women who experienced a stillbirth
33
34 134 found that 30% had noted significant RFM prior to the diagnosis of stillbirth¹⁰.
35
36 135 Although the mechanisms have not been fully delineated, it is likely that RFM and
37
38 136 stillbirth are linked by a common pathology, that of placental dysfunction¹¹. There is
39
40 137 good evidence linking placental dysfunction and RFM. Compared to controls with an
41
42 138 active fetus women who have fewer fetal movements on ultrasound scan immediately
43
44 139 prior to caesarean section are more likely to have umbilical cord gas measurements
45
46 140 indicative of acidaemia, hypoxaemia, and hypercapnia¹². Women delivering within
47
48 141 one week of an episode of RFM show differences in placental structure and function
49
50 142 which are reminiscent of those seen in fetal growth restriction (FGR) and stillbirth^{13 14}.
51
52 143 Additionally, the odds of fetal growth restriction (FGR, defined as being at less than
53
54 144 the 10th centile for gestation adjusted birthweight) were greater in women with RFM
55
56 145 compared with controls (adjusted OR 1.6, 95% CI 1.1–2.2¹⁵). Taken together these
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3 146 data are strong evidence that placental dysfunction is associated with RFM, and a
4
5 147 causative pathway seems likely.

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7 148 The evidence linking placental dysfunction and stillbirth is even stronger; a systematic
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9 149 review of placental pathology in stillbirths described abnormalities in up to 65% of
10
11 150 cases ¹⁰. Amongst the 291 stillbirths in Scotland in 2010, 137 (47%) had evidence of
12
13 151 placental dysfunction ¹⁶. Given that the placenta was examined in only 80% of
14
15 152 stillbirths, the true prevalence of placental dysfunction is likely to be higher. In
16
17 153 addition, between 20%-40% of stillborn babies are reported to have FGR, as defined
18
19 154 by a birthweight less than the 10th centile ¹⁷. Additionally, the Lancet report notes that
20
21 155 “placental pathologies accounted for one in four deaths across all gestational ages,
22
23 156 and were contributory or causal in more than half of cases” ⁶. Given that stillbirth is
24
25 157 strongly related to placental dysfunction, and RFM is a “biomarker” of placental
26
27 158 dysfunction then better management of women presenting with RFM focussing on the
28
29 159 detection of placental dysfunction might reduce the risk of stillbirth.

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32 160

33 161 *Formal Fetal Movement Counting*

34
35 162 Although prenatal detection of FGR is improved by fetal movement counting ¹⁸, a
36
37 163 systematic review ¹⁹, and a large and influential cluster randomised trial (which
38
39 164 dominates the systematic review) showed that routine fetal movement counting using
40
41 165 the count to ten charts had no effect on perinatal mortality ²⁰. Thus, the National
42
43 166 Institute for Health and Social Care Excellence (NICE) recommended that “Routine
44
45 167 formal fetal movement counting should not be offered” ²¹. Importantly, the large
46
47 168 cluster randomised trial tested a specific alarm limit for RFM, but did not recommend
48
49 169 a specific management strategy for women who did present with RFM. There were
50
51 170 two important observations from this study, firstly that in both groups the perinatal
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53 171 mortality rate was lower than contemporary or subsequent periods in the UK and
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55 172 secondly that more women in the fetal movement counting arm came in with a live
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57 173 baby who subsequently died compared with the control arm (19 vs 11), suggesting

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3 174 that one reason the strategy failed to reduce perinatal mortality was inadequate
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5 175 investigation and management of those presenting with RFM ²⁰.

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9 177 *Optimal strategy for determining RFM to prompt maternal presentation to the*
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11 178 *maternity service*

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13 179 Maternal concern about RFM is a common reason to contact maternity services with
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15 180 between 6-15% of women presenting during the third trimester.^{22 23} Nevertheless,
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17 181 delays in reporting RFM to maternity care providers may increase the risk of adverse
18
19 182 outcome.^{24 25} The lack of good-quality information given to women about fetal
20
21 183 movements has been highlighted as an example of suboptimal care in Confidential
22
23 184 Enquiries into Antepartum Stillbirth.^{26 27} Qualitative studies suggest that women
24
25 185 frequently perceive RFM two days prior to the diagnosis of fetal death, and in some
26
27 186 cases contractions were misinterpreted as fetal movements.²⁸ Therefore, giving
28
29 187 information to women regarding fetal movements and when they should be
30
31 188 concerned about RFM is a key component of an intervention to reduce stillbirth.

32
33 189 However, giving clear information about RFM can be challenging as there is no
34
35 190 uniform threshold of fetal movements below which perinatal morbidity increases ²³,
36
37 191 and no evidence that a specific threshold performs better than maternal perception of
38
39 192 reduced fetal movements alone ⁸. Current guidelines from the RCOG and PSANZ ²⁹
40
41 193 ³⁰, informed by a large Norwegian study ³¹ suggest that it is *maternal perception* of
42
43 194 decreased fetal movement which is important. Therefore, information for pregnant
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45 195 women in this study (shown in Supplementary File 1) described the importance of
46
47 196 fetal movements, the need to get to know normal fetal activity, how fetal movements
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49 197 change in late pregnancy and who to contact if the mother perceives RFM. The
50
51 198 educational package aimed to ensure that these messages were reinforced by staff
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53 199 behaviour at antenatal contacts.

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57
58 201 *Optimal strategy for investigation and management of women presenting with RFM.*
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1
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3 202 A recent systematic review found there are no proven strategies for the investigation
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5 203 and management of women presenting with RFM ³². Cardiotocography (CTG) is
6
7 204 routinely used to ascertain fetal wellbeing, and it is the cornerstone of the RCOG
8
9 205 guideline ³⁰. However, data from Norway, suggests that ultrasound assessment of
10
11 206 fetal size is often the most helpful investigation, performing well on both an absolute
12
13 207 basis, and compared with other interventions ³³. In a series of over 3,000 women with
14
15 208 RFM, ultrasound (including measurement of fetal biometry and liquor volume) was
16
17 209 found to be useful in detecting abnormalities in 11.6% of scans. In 71% of women in
18
19 210 whom an abnormality was found, ultrasound was the only technique that detected an
20
21 211 abnormality. Additionally, 85% of abnormalities detected by ultrasound, were
22
23 212 important in informing the clinical management of the woman ³³. These data are
24
25 213 supported by a smaller UK study which found that abnormalities detected on CTG or
26
27 214 ultrasound scan were most strongly associated with adverse outcome in women with
28
29 215 RFM, with identification of abnormal estimated fetal growth centile on scan being the
30
31 216 test most highly predictive of poor outcome ³⁴. Perhaps this is not surprising, given the
32
33 217 strong association between RFM and placental dysfunction and the central
34
35 218 importance of ultrasound in the identification and management of small for gestational
36
37 219 age babies ³⁵. Given these data, it is concerning that a survey of clinicians in Scotland
38
39 220 showed that fewer than 5% would routinely refer women with RFM for ultrasound
40
41 221 examination (unpublished data from June 2012), and a survey of 223 UK midwives
42
43 222 and obstetricians described that 17.9% of respondents would perform an ultrasound
44
45 223 scan ³⁶. These views of clinicians may reflect the variable quality of local guidelines,
46
47 224 which are frequently not based on national recommendations, even those for which
48
49 225 there is strong evidence ³⁷. The variation in information given to women and
50
51 226 subsequent management of RFM has been highlighted as sources of suboptimal care
52
53 227 in two confidential enquiries into antepartum stillbirth ^{26 27}. Therefore, we believe that
54
55 228 current investigation of women presenting with RFM is inadequate, hence using the
56
57 229 best available evidence, we have drafted what we consider to be a robust evaluation
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3 230 protocol for investigation of women with RFM.
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5 231 *Potentially efficacy of a package of intervention for RFM*
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7 232 Supportive data for the package of interventions used in this study (information for
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9 233 women and standardised management protocol) comes from a large observational
10
11 234 “clinical quality improvement study” in Norway which found a significant fall in rates of
12
13 235 stillbirth (from 3.0/1,000 to 2.0/1,000 [OR 0.67 95% CI 0.48–0.93]) after the
14
15 236 introduction of an intervention package consisting of written information for women
16
17 237 about awareness of RFM combined with consensus guidelines for health
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19 238 professionals about their management ³¹. Although this study was not randomised,
20
21 239 and therefore constitutes only level II-3 evidence, it has informed recommendations
22
23 240 from the Royal College of Obstetricians and Gynaecologists (RCOG) and Perinatal
24
25 241 Society of Australia and New Zealand (PSANZ) that “women should be advised to be
26
27 242 aware of their baby’s individual pattern of movements and that if they are concerned
28
29 243 about a reduction in or cessation of fetal movementsthey should contact their
30
31 244 maternity unit” ^{29 30}. Following initial publication of the Norwegian study, a re-analysis
32
33 245 was required as discrepancies between stillbirth rates in the study and the Medical
34
35 246 Birth Registry of Norway were identified. This reanalysis found the reduction in
36
37 247 stillbirth rates was of borderline statistical significance (OR 0.72, 95% CI 0.50-1.03).
38
39 248 The authors concluded that further studies were needed to determine whether this
40
41 249 approach was associated with a reduction in stillbirth ³⁸.
42
43 250 Importantly, in the Norwegian study, there was no increase in the proportion of
44
45 251 women who presented with RFM when rates were compared before and after the
46
47 252 intervention ³¹. However, women with RFM presented significantly earlier to hospital
48
49 253 than they had hitherto, potentially allowing time for intervention to reduce perinatal
50
51 254 mortality. These data suggest that a package of interventions encouraging women
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53 255 with RFM to present early to hospital, combined with a structured approach to their
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55 256 management might reduce rates of stillbirth without contributing to a large increase in
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57 257 admissions antenatally.
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5 259 *Potential harms of a package of care around increased awareness and optimised*
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7 260 *management of RFM*

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10 261 Any clinical intervention which aims to improve outcomes also has the ability to do
11
12 262 harm. Thus, it is essential that the intervention proposed is rigorously evaluated using
13
14 263 the gold standard technique of a randomised trial, rather than being introduced as a
15
16 264 service development. When the study began, there was a small window of
17
18 265 opportunity to do this, as the enthusiasm to improve current management of RFM is
19
20 266 such that routine introduction of the package of care is unlikely to be delayed much
21
22 267 further than the current scheduled end date of this study. Possible harms of a
23
24 268 package of care consisting of a management plan for identification and delivery of the
25
26 269 “at risk” fetus, together with strategies for increasing pregnant women’s awareness of
27
28 270 the need to report early include increased maternal anxiety and increased
29
30 271 intervention (including hospital admission, induction of labour and Caesarean section)
31
32 272 which itself is associated with pregnancy related complications. The available
33
34 273 evidence is reassuring on some of these issues. A systematic review of 23
35
36 274 publications from 16 studies found three studies involving 2,030 women addressing
37
38 275 maternal concern and an additional three studies involving 1,468 women investigating
39
40 276 maternal-fetal attachment. These demonstrated no evidence of increased maternal
41
42 277 anxiety and results regarding maternal-fetal attachment were discordant.³⁹ In the
43
44 278 Norwegian service development study, the package of care increased rates of follow
45
46 279 up of women, but there was no increase in admissions overall, admissions for
47
48 280 induction or admissions for emergency caesarean section ³¹ – again, whilst
49
50 281 reassuring these outcomes require formal evaluation in a randomised and relevant
51
52 282 setting to the UK and Republic of Ireland. The final possible harm of the package is
53
54 283 around increased resource use, and the opportunity cost of focussing on RFM rather
55
56 284 than other potential methods to prevent stillbirth.

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RATIONALE

The aim of this study is to test the hypothesis that a package of interventions consisting of strategies for increasing pregnant women's awareness of the need to report early when they perceive a reduction in fetal movements, followed with a management plan for identification and delivery of the "at risk" fetus in such women, will reduce rates of stillbirth.

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STUDY OBJECTIVES*Primary Objective*

The primary objective is to answer the research question 'Does the introduction of a protocol for detection and management of decreased fetal movements reduce rates of stillbirth?' The secondary objectives are to answer the following research questions:

- What is the effect of the intervention on rates of caesarean section and induction of labour?
- What is the effect of the intervention on rates of admission to the neonatal intensive care unit?
- What is the effect of the intervention on the proportion of women with FGR remaining undelivered by 40 weeks gestation?
- What is the acceptability of such a package of care to pregnant women and their health care providers?
- What other process outcomes are influenced by the intervention, such as health care provider/patient interactions?

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3 310 **ENDPOINTS**
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5 311 *Primary Outcome*
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8 312 The primary endpoint is stillbirth (antepartum and intrapartum). We will use the UK
9
10 313 definition of stillbirth which is “a baby delivered without signs of life after 23⁺⁶ weeks”
11
12 314 ⁴. Where gestation is uncertain we will include all babies with a birth weight of 500g
13
14 315 or more.

15
16 316 *Secondary Endpoints*
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19 317 Other measures of perinatal mortality including:
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- 21 318 • Stillbirth at 37 weeks gestation and above
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23 319 • Stillbirth at 28 weeks gestation and above (WHO definition of stillbirth)
24
25 320 • Stillbirth at 22 weeks gestation and above (international stillbirth alliance
26
27 321 definition)
28
29 322 • Stillbirths amongst normally formed infants of 22 weeks gestation and above,
30
31 323 24 weeks gestation and above, 28 weeks gestation and above and 37 weeks
32
33 324 gestation and above.
34
35 325 • Perinatal mortality (defined as stillbirth at 24 weeks gestation and above and
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37 326 deaths in the first seven days of life)
38
39 327 • Rates of caesarean section
40
41 328 • Rates of induction of labour (for any indication)
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43 329 • Rates of elective delivery (induction of labour and caesarean section prior to
44
45 330 the onset of labour) overall
46
47 331 • Rates of induction of labour at 39 weeks gestation or later
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49 332 • Mean gestation at induction of labour
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51 333 • Rates of admission to the neonatal unit (and their reasons)
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3 334 • Rates of admission to the neonatal unit for more than 48 hours
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5 335 • Rates of admission to the neonatal unit for term babies (those born at 37
6 weeks 0 days or greater)
7 336
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9
10 337 • Proportion of infants with fetal growth restriction (less than the 5th centile,
11 customised for gender) remaining undelivered at or after 40 weeks gestation
12 338
13
14 339 • Birthweight centile (according to the Intergrowth birthweight centile calculator
15 at <https://intergrowth21.tghn.org>)
16 340
17
18 341 • Rates of spontaneous vaginal delivery
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20
21
22 342 Other secondary outcomes are the baby parameters:
23
24 343 • Gestation at birth
25
26 344 • Proportion of babies born preterm (<37 weeks gestation)
27
28 345 • Gender of the baby
29
30 346 • Birthweight of the baby
31
32 347 • Apgar score at 5 minutes
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34 348 • Proportion of babies with 5 minute Apgar score < 7
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36 349 • Proportion of babies with 5 minute Apgar score < 4
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38 350 • Resuscitation required at birth
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45 351 We will also collect the following data: maternal age, maternity unit of delivery,
46 352 birthweight, gestation of delivery, parity, gestation, sex, smoking (current and ever),
47 353 maternal body mass index (BMI), number of babies (one or more), ethnicity (to allow
48 354 a customised birthweight centile to be generated), method of delivery, deprivation
49 355 category (where available) and other neonatal variables including Apgar score and
50 356 encephalopathy. Adjustment will be made for the following variables: (maternal age,
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3 357 maternity unit of delivery, parity, smoking status, maternal BMI, number of babies
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5 358 [one or more] and ethnicity)

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10 360 **STUDY DESIGN**

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12 361 This is a multicentre, stepped wedge cluster randomised trial of a package of care
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14 362 consisting of a management plan for identification and delivery of the 'at risk' fetus,
15
16 363 together with strategies for increasing pregnant women's awareness of the need to
17
18 364 report RFM early. The trial developed from a planned quality improvement project
19
20 365 proposed by the Scottish Government to reduce stillbirths. This was planned to
21
22 366 emphasise the importance of fetal movement monitoring and was to be rolled out to
23
24 367 all NHS maternity units in Scotland. However, prior to this change it was agreed that
25
26 368 the roll out could be performed in such a way as to allow the assessment of the effect
27
28 369 of the intervention, the stepped-wedge design would be the natural choice in this
29
30 370 circumstance.

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32
33 371 The study will take place in participating hospitals in the UK and Ireland (a complete
34
35 372 list is available <http://www.crh.ed.ac.uk/affirm/randomised-hospitals/>). A nested
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37 373 qualitative study will examine the acceptability of the intervention to patients and
38
39 374 health care providers and identify process issues (barriers to implementation).
40
41 375 Clinical audit (detailed in Appendix 3) conducted after the change in practice will be
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43 376 used to determine the effect of interventions on process outcomes (e.g. number of
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45 377 women presenting with reduced fetal movements, interval between perceiving
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47 378 reduced fetal movements and presentation to hospital, number of ultrasound scans,
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49 379 number of admissions for induction of labour). A diagram indicating randomisation of
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51 380 hospital groupings in the stepped wedge design is shown in Figure 1.

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54 381 The interventions will be introduced over a 32 month period. Data will be collected
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56 382 over a 36 month period. Data in the 'active phase' after introduction of the
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3 383 intervention will be compared to data in the ‘control phase’ – the period during which
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5 384 usual care processes in study sites are followed from study start to the time of
6
7 385 introduction of the intervention. Given that it will take individual units some time (a) to
8
9 386 effect change in management in their unit from time of introduction of the intervention
10
11 387 and (b) that it will take some time for this change in practice to impact on clinical
12
13 388 outcomes, we plan a “washout” period of two months after the introduction of the
14
15 389 intervention during which data will not be included in either group for analysis (Figure
16
17 390 1). Data will be collected four months after the last birth, a further two months has
18
19 391 been included for data analysis, giving a total study duration of 42 months.
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22 392

23 24 393 **STUDY POPULATION**

25 26 27 394 *Number of participants*

28
29 395 Participants will be those delivering at all the sites over the study period (36 months).
30
31 396 All eligible women will be recruited to the cluster randomised controlled trial. Based
32
33 397 on previous delivery numbers, after accounting for a washout period of two months
34
35 398 (and assuming no withdrawals or losses to follow up) this is estimated to be a total of
36
37 399 around 143,140 women per annum. A subset of around 30 participating women and
38
39 400 30 midwives, sonographers and obstetricians will be recruited to the nested
40
41 401 qualitative study, which is based in the Scottish sites.
42
43

44 402 *Inclusion criteria*

45
46 403 We will include all women delivering at one of the participating maternity units for the
47
48 404 duration of the study. Women who have been seen at any of the maternity units but
49
50 405 who deliver at home will not be included. The duration of the study will be 42 months
51
52 406 from the start of the trial (01/02/2014). For practical reasons, participants for the
53
54 407 nested qualitative study will be recruited from the participating units in Scotland.
55
56

57 408 *Exclusion criteria*

58
59
60

1
2
3 409 We will exclude women as follows:
4

5 410 • Women for whom data on delivery outcomes is still unavailable four months after
6
7 411 the date of delivery
8

9
10 412 • Women delivering in the “washout” period in each unit.
11

12 413 Members of the trial management group and participants who do not
13 414 speak/understand English will be excluded from participating in the nested qualitative
14
15 415 study.
16

17
18
19 416 *Identifying participants*
20

21 417 Women will be identified from those whose data is included in routine data returns
22
23 418 from each unit. Potential participants for the nested qualitative study will be identified
24
25 419 from those attending antenatal clinics in participating hospitals, and/or local staff.
26
27

28 420 *Consenting participants*
29

30
31 421 The main study is a stepped wedge cluster randomised trial of a package of care
32
33 422 which would be introduced in many of the participating units regardless of whether
34
35 423 the trial was on-going or not and the trial uses only routinely collected data on
36
37 424 participants. The ethics committee indicated that formal individual patient consent is
38
39 425 not necessary for the main trial. Participants in the nested qualitative study will be
40
41 426 asked for individual consent.
42

43 427 *Screening for eligibility*
44

45
46 428 As participants are not directly recruited we will not perform any specific screening
47
48 429 tests for this aspect of this project. Participants for the nested qualitative study will
49
50 430 be: (i) Pregnant women attending hospitals who are participating in the main trial in
51
52 431 Scotland. Purposive sampling will ensure that the final sample set includes women
53
54 432 who have and who have not experienced RFM, both before and after the introduction
55
56 433 of the intervention; (ii) Hospital staff (including midwives, ultrasonographers and
57
58
59
60

1
2
3 434 obstetricians/radiologists) working in participating hospitals in Scotland. There will be
4
5 435 no specific screening tests for eligibility for the nested qualitative study, except that
6
7 436 women who have experienced a stillbirth in the index pregnancy will not be
8
9 437 approached.

10
11 438 *Ineligible and non-recruited participants*

12
13
14 439 Potential participants for the nested qualitative study who are not approached or who
15
16 440 decline will have no specific interventions / procedures.

17
18
19 441 *Withdrawal of Study Participants*

20
21 442 The nature of a cluster randomised study is such that it is not possible for the
22
23 443 participant to withdraw from the “cluster” unless she changes maternity unit part way
24
25 444 through her pregnancy. We plan to collect routinely recorded anonymised data;
26
27 445 patients have the right to opt out of having their data used – if this happens their data
28
29 446 would be excluded from the study database (e.g. under the Confidentiality and
30
31 447 Security advisory Group Report 2002 and the Data Protection Act (1998)
32
33 448 requirements for fair processing of data). Participants in the nested qualitative study
34
35 449 who wish to withdraw will be allowed to do so. Their data will be retained and used,
36
37 450 unless they additionally indicate that they wish to withdraw their data.

38
39
40 451 **RANDOMISATION**

41
42 452 *Randomisation Procedures*

43
44
45 453 This is a cluster-randomised, stepped-wedge design trial wherein maternity units
46
47 454 rather than individual patients are randomised. All units will implement the fetal
48
49 455 movement monitoring intervention at some point during the trial; the random element
50
51 456 is the time point at which this will occur, the so-called “step” of the stepped-wedge
52
53 457 design. Participating maternity units will be blinded to their randomly allocated time
54
55 458 point until the time this is required to be revealed to enable the necessary training in
56
57 459 the implementation of the intervention to be delivered. Primary and secondary
58
59
60

1
2
3 460 outcomes of the trial will be gathered in a blinded manner via routinely collected data
4
5 461 sources.

6
7 462 Maternity units which are in close proximity to each other will be grouped for the
8
9 463 purposes of randomisation. This will assist with the feasibility of delivering the training
10
11 464 for and implementation of the intervention. Furthermore, this local synchronisation of
12
13 465 the intervention implementation will minimise the chances of contamination
14
15 466 (introduction of the intervention prematurely) from maternity units which have already
16
17 467 implemented the intervention to those not yet randomised.

18
19
20 468 The order in which the groups of maternity units step in to implement the intervention
21
22 469 will be determined by computer generated random numbers from a uniform
23
24 470 distribution. The randomisation list will be held by the Edinburgh Clinical Trials Unit
25
26 471 (ECTU). The identities of the research team staff whose roles in the trial require them
27
28 472 to be unblinded to randomisation codes will be recorded in the trial master file (TMF).

29
30
31 473 *Treatment Allocation*

32
33 474 Participating sites will be randomised to different schedules for implementing the
34
35 475 intervention. All units will be providing conventional treatment at baseline according
36
37 476 to local practice – this is the treatment established before the study starts. Sites will
38
39 477 be randomised to “active” treatment in turn as described above. Active treatment will
40
41 478 consist of a package of care consisting of a management plan for identification and
42
43 479 delivery of the ‘at risk’ fetus, together with strategies for increasing pregnant women’s
44
45 480 awareness of the need to report RFM early. The recommended management plan for
46
47 481 identification and delivery of the “at risk” fetus is shown in Figure 2. Practice change
48
49 482 in the active units will be achieved by: (i) written/email information to all clinicians
50
51 483 (doctors, midwives and ultrasonographers) in each unit about the study protocol and
52
53 484 amendment of the local protocol for Reduced Fetal Movements (RFM) to that of the
54
55 485 study protocol; (ii) a short web-based training package taking approximately one hour
56
57 486 to complete for all clinicians in each centre and (iii) training /information sessions to
58
59
60

1
2
3 487 run in each unit and (iv) posters in each unit to describe the practice change.
4
5 488 Strategies for encouraging clinicians to increase pregnant women's awareness of
6
7 489 fetal movement will include all the above and also a fetal movement leaflet for
8
9 490 pregnant women (shown in Supplementary Information 1). The Norwegian quality
10
11 491 improvement study showed inconclusive results regarding the effect of the
12
13 492 intervention in non-European women.⁴⁰ To attempt to address this, the AFFIRM
14
15 493 information leaflet was available in 12 languages including: Arabic, Bengali, English,
16
17 494 Hindi, Hungarian, Latvian, Lithuanian, Mandarin, Polish, Russian and Urdu.
18
19 495 Furthermore, by including staff education which highlighted the need to ask women
20
21 496 about fetal movements in routine antenatal consultations as many women as
22
23 497 possible should have received information about what to do if they perceive RFM.
24
25
26 498 Once units have begun active treatment it is not anticipated that they will return to
27
28 499 conventional treatment. We will conduct an audit of women presenting with reduced
29
30 500 fetal movements and assess the proportion of staff completing the online training to
31
32 501 assess the extent to which sites have followed the intervention plan. Units will be
33
34 502 informed about treatment allocation as near as possible to the implementation of the
35
36 503 "active" treatment. For practical purposes, we anticipate that each unit will need
37
38 504 around three months' notice before the "active" treatment is introduced, hence units
39
40 505 will be informed of the timing of their treatment allocation (step) three months before
41
42 506 the active treatment is due to start. The treatment allocation will not be administered
43
44 507 blind and there are no restrictions on concomitant care or other interventions during
45
46 508 the study, hence there is no need for emergency unblinding and there are no
47
48 509 stopping rules for the study.

50
51 51052
53 **511 DATA COLLECTION**54
55
56 512 For the main trial, data will be accessed from the information routinely collected
57
58 513 during the clinical management of the patient. For consistency, we will normally only
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60

1
2
3 514 include data items which become available within four months after the delivery date
4
5 515 in question, although we may seek advice from the independently-chaired trial
6
7 516 steering committee (TSC) about exceptions as they arise. Different data sources will
8
9 517 be used for different regions of the study: (i) In Scotland the source data will be
10
11 518 SMR2 and the Scottish Birth record, (ii) In Ireland the source data will be the National
12
13 519 Perinatal Reporting System (NRPS http://www.esri.ie/health_information/nprs), (iii) In
14
15 520 Northern Ireland, the source data will be the Northern Ireland maternity Statistics
16
17 521 database (NIMATS), (iv) In England and Wales, the source data will be the ONS, or
18
19 522 other relevant body. Data will be collected retrospectively on an annual basis from all
20
21 523 sources. We will assume that data unavailable four months after the woman
22
23 524 delivered is likely to be unobtainable (but see note in Study Design section above).
24
25 525 Thus, data on the first year of the study will be collected at month 16; data on the
26
27 526 second year will be collected at month 28 etc.

28
29
30 527 Data are routinely collected. A formal request for data access will be made at the
31
32 528 start of the study. This will require (i) in Scotland – Privacy Advisory Committee
33
34 529 approval and a formal approach to NHS Scotland Information Services Division (ISD)
35
36 530 (ii) in Ireland a formal approach to NRPS (iii) NIMATS in Northern Ireland (iv) in
37
38 531 England and Wales a formal approach will be made to the relevant bodies.

39
40 532 Data will then be sent to the electronic Data Research and Innovation Service
41
42 533 (eDRIS) National Safe Haven (NHS National Services Scotland) by secure file
43
44 534 transfer protocol (or other similar) for storage and subsequent analysis within a
45
46 535 secure project area (dedicated to the AFFIRM study). Further information on the
47
48 536 National Safe Haven is available at [http://www.isdscotland.org/Products-and-](http://www.isdscotland.org/Products-and-Services/eDRIS/Becoming-an-eDRIS-User/#NSS-National-Safe-Haven)
49
50 537 [Services/eDRIS/Becoming-an-eDRIS-User/#NSS-National-Safe-Haven](http://www.isdscotland.org/Products-and-Services/eDRIS/Becoming-an-eDRIS-User/#NSS-National-Safe-Haven). Briefly, the
51
52 538 National Safe Haven is located on a secure server, in which trusted and authorised
53
54 539 researchers can analyse individual level data while maintaining the utmost
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1
2
3 540 confidentiality. It is anticipated that all study analysis will be done within the Safe
4
5 541 Haven, using one of the available statistical packages (e.g. R, SPSS).

6
7 542 Identifiers on Scottish data within the National Safe Haven are concealed from
8
9 543 researchers. Data from outwith Scotland will be anonymised before submission to the
10
11 544 National Safe Haven. We propose that data submitted to the National Safe Haven
12
13 545 will be “anonymised” by the data provider. However, we propose that the
14
15 546 anonymisation link will be retained at the source so that it will be possible to re-link
16
17 547 data retrospectively. The rationale for retaining the ability of local data guardians to
18
19 548 re-link data is because it is important to retain the possibility of identifying individual
20
21 549 patients retrospectively. Examples include: (i) It is possible that some additional
22
23 550 important data may be available at a late stage on individual participants – e.g. in the
24
25 551 scenario where the woman or baby had a major adverse event and spent a long time
26
27 552 in hospital before discharge or death and (ii) Although our protocol and outcome
28
29 553 analysis does not require identifiable data, we believe this will be a ‘once in a lifetime’
30
31 554 study, and that subsequent secondary analyses could yield important information for
32
33 555 patients and for policy makers. If retrospective identification is not possible, this will
34
35 556 limit further analysis. One likely example of future analyses is to determine the effect
36
37 557 of the intervention on different causes of stillbirth. This is outwith the scope of the
38
39 558 current protocol, but could be done relatively straightforwardly, by linking nationally
40
41 559 recorded information on “cause” of stillbirth to our study database. We anticipate that
42
43 560 such additional analyses would require additional ethics approval, but without a
44
45 561 process by which to re-link data, it will not be possible to perform such subsequent
46
47 562 analyses.

48
49
50 563 All Investigators and study site staff involved with this study will comply with the
51
52 564 requirements of the Data Protection Act 1998 (or equivalent for those outwith the UK)
53
54 565 with regard to the collection, storage, processing and disclosure of personal
55
56
57
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60

1
2
3 566 information and will uphold the Act's core principles. Published results will not contain
4
5 567 any personal data that could allow identification of an individual participant.
6

7
8 568 In addition to the data recorded above, all sites will be asked to provide a copy of
9
10 569 their guidelines around (i) maternal awareness of RFM and (ii) management of
11
12 570 women presenting with RFM. Copies of guidelines will be sought by the study office
13
14 571 (a) at the start of the study (b) immediately before initiation of the intervention in each
15
16 572 specific unit and (c) six months after initiation of the intervention in each specific unit.
17

18 573 For the nested qualitative study, we will perform interviews of healthcare workers and
19
20 574 a small nested cohort of pregnant women about their experiences of fetal movement
21
22 575 and of this intervention. We shall ensure a diversity of age and include nulliparous
23
24 576 and multiparous women (n=30 in total). Ten interviews will be conducted with each of
25
26 577 the following groups of health care providers: obstetricians, midwives and
27
28 578 sonographers/radiologists. The interviews will take a semi-structured format
29
30 579 (sensitising and piloting interviews will be conducted prior to the commencement of
31
32 580 the trial and in the first month of the nested qualitative study). This format will ensure
33
34 581 the same categories of data will be obtained from each participant but also allow
35
36 582 individual responses to be fully explored.
37

38
39 583

40 41 584 **STATISTICS AND DATA ANALYSIS**

42 43 585 *Sample size calculation*

44
45
46 586 The sample size is the number of women delivering in hospitals participating in the
47
48 587 study. This was initially planned to include sites in Scotland, totalling around 58,000
49
50 588 deliveries per year with 16 consultant led maternity units, 20 smaller units each
51
52 589 delivering less than 350 babies per year, and seven units delivering less than five
53
54 590 births per year. The units involved in Perinatal Ireland (an all-Ireland research
55
56 591 consortium across 7 academic sites in Ireland currently funded by the Health
57
58
59
60

1
2
3 592 Research Board, Ireland) have 50,000 births per year with seven large sites.
4
5 593 Combining one or two of the smaller units and one larger unit into a single “hospital
6
7 594 group” for each local area could provide 24 hospital “groups” – the details of hospital
8
9 595 groupings will be reviewed and finalised immediately prior to randomisation. In total,
10
11 596 36 sites expressed interest in participating in the study, although 2 were unable to
12
13 597 participate in the study and withdrew before randomisation. In total, 34 units were
14
15 598 randomised, these were situated throughout the UK and Ireland (10 in England, 4 in
16
17 599 Ireland, 15 in Scotland and 5 in Wales) with 143,140 births per annum.

18
19
20 600 We calculated statistical power using the methodology for stepped wedge designs
21
22 601 proposed in Hussey and Hughes (2007).⁴¹ First, we analysed stillbirth event data
23
24 602 from the Scottish Perinatal and Infant Mortality and Morbidity Report (SPIMMR)
25
26 603 covering years 2005-2010 ¹⁶ to determine estimates of between- and within-unit
27
28 604 variability in stillbirth rate. Analysis was by generalized linear mixed model for binary
29
30 605 outcomes. The power calculation, as per equations (#7) and (#8) in ⁴¹ assumed:
31
32 606 significance level 5%; analysis by generalized linear mixed model; deliveries equally
33
34 607 distributed across hospital groupings; baseline stillbirth rate 0.438% ¹⁶; cluster
35
36 608 coefficient of variation 0.333.

37
38
39 609 Finally, the statistical power depends on the number of groups in which the
40
41 610 intervention is implemented at each stage of the stepped wedge design and the
42
43 611 duration of recruitment at each “step”. Our study design proposes sequential
44
45 612 introduction of the intervention into three hospital groups at a time in eight steps at
46
47 613 four month intervals. This would give 92.4% power to detect a 30% risk reduction
48
49 614 under the intervention and 80.7% power to detect a 25% reduction. A 30% risk
50
51 615 reduction was seen in the Norwegian study; the anticipated effect sizes of 25% and
52
53 616 30% relative reduction take into account that the intervention will not have the power
54
55 617 to reduce all stillbirths, since 20% of stillbirths in Ireland ⁴² and 15% in Scotland ¹⁶ are
56
57 618 associated with congenital anomaly.

1
2
3 619 The power actually achieved in the study will be slightly lower, as deliveries during
4
5 620 the two month “transition” period following implementation of the intervention in a site
6
7 621 will not be included in the analysis. The effect of this was explored using the Stata
8
9 622 function steppedwedge,⁴³ which showed the statistical power would become 88.2%
10
11 623 (30% risk reduction) and 74.6% (25% risk reduction). It is anticipated that
12
13 624 unavailability of data and women asking to withdraw their data will be less than 1%.

14
15 625 *Proposed analyses*

16
17
18 626 For the binary primary and secondary outcomes, data will be analysed by
19
20 627 generalized linear mixed model with a random effect for hospital and fixed effects for
21
22 628 the intervention implementation and study time period. A site by intervention
23
24 629 interaction random effect will be included in the model and retained if it explains an
25
26 630 important proportion of the variability in outcomes. The primary analysis of data will
27
28 631 be on an intention to treat basis (the design of the trial means it is not possible to
29
30 632 determine individual patient /caregiver compliance with the intervention). An “on
31
32 633 treatment” variable will be calculated for which women will be grouped as active or
33
34 634 control according to when the intervention was actually implemented in their site,
35
36 635 instead of when the site was randomised to implement the intervention. The primary
37
38 636 outcome will be reanalysed in two sensitivity analyses. Firstly, we will perform the
39
40 637 analysis according to the actual timing of the implementation of the intervention
41
42 638 rather than the randomised timing of the intervention using the “on treatment”
43
44 639 classification. Secondly, we will perform the analysis in the subgroup of sites who
45
46 640 were deemed to have implemented the intervention effectively according to the
47
48 641 perception of the Principal Investigator at each site. The accuracy of this perception
49
50 642 will be confirmed with the findings of a site audit (details in Appendix 3). There will be
51
52 643 no attempt to correlate the impact of the intervention according to the results of the
53
54 644 site audit.
55
56
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1
2
3 645 There are no planned imputations for missing data. However, if the missing data rate
4
5 646 for smoking status during pregnancy is relatively high an imputation technique will be
6
7 647 devised. The imputation method will be informed using smoking history at booking
8
9 648 and age at delivery ⁴⁴. A pre-specified subgroup analysis will be performed for babies
10
11 649 with and without congenital anomalies, and will be implemented by testing for an
12
13 650 intervention by congenital anomaly interaction added to the generalised linear mixed
14
15 651 model described above. No formal interim analyses for efficacy or safety will be
16
17 652 performed. A full statistical analysis plan will be finalised prior to locking of the study
18
19 653 database.

20
21 654 *Qualitative Data*

22
23
24 655 For the nested qualitative study, the data will be audio recorded and transcribed.
25
26 656 The data will be coded thematically and an analytical framework developed to make
27
28 657 sense of patient experience of fetal movement and the intervention and also health
29
30 658 care providers' perspectives and experiences. NVivo will be utilised to support the
31
32 659 analysis.

33
34
35 660 *Process outcomes*

36
37 661 The process outcomes being assessed by the (rates of induction of labour, number
38
39 662 of women presenting with reduced fetal movements, interval between perceiving fetal
40
41 663 movements and presenting to hospital) will be analysed using the same methods as
42
43 664 for the main trial, with the exception of the continuous outcome (interval between
44
45 665 perceiving fetal movements and presenting to hospital) which will be analysed using
46
47 666 a normal linear mixed model.

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51
52 668 **ADVERSE EVENTS**

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54
55 669 This is not a Clinical Trial of an Investigational Medicinal Product (CTIMP) so adverse
56
57 670 events will not be formally reported. Stillbirth and other measures of fetal and
58
59
60

1
2
3 671 maternal morbidity are outcomes of the study. The purpose of the intervention is to
4
5 672 reduce such adverse events. Therefore, due to the low risks for this trial, a separate
6
7 673 DMC is not required and the Trial Steering Committee (TSC) will cover any
8
9 674 responsibilities normally allocated to a DMC. If considered necessary, the TSC may
10
11 675 review unblinded data for the study, including morbidity and mortality indices. No
12
13 676 other adverse event reporting will be undertaken.

14
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16 677

17 678 **TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS**

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19
20 679 The trial will be coordinated by a Project Management Group, consisting of the grant
21
22 680 holders and the Trial Manager. The Chief Investigator (JN) will lead the project
23
24 681 management group. The Trial Manager will oversee the study and will be
25
26 682 accountable to the Chief Investigator. A TSC will be established to oversee the
27
28 683 conduct and progress of the trial. The terms of reference and a draft template for
29
30 684 reporting will be ratified in one of the early meetings of the TSC.

31
32
33 685 Investigators and institutions involved in the study will permit trial related monitoring
34
35 686 and audits on behalf of the co-sponsors (ACCORD: Academic and Clinical Central
36
37 687 Office for Research & Development - Joint office for University of Edinburgh and
38
39 688 NHS Lothian, Sponsor contact: ray.french@ed.ac.uk), research ethics committee
40
41 689 (REC) review, and regulatory inspection(s). In the event of an audit or monitoring, the
42
43 690 Investigator agrees to allow the representatives of the sponsor direct access to all
44
45 691 study records and source documentation. In the event of regulatory inspection, the
46
47 692 Investigator agrees to allow inspectors direct access to all study records and source
48
49 693 documentation.

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3 696 *Study monitoring and audit*
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5 697 The sponsor determined that as no individual participants were recruited to the
6
7 698 intervention, and it was not a clinical trial of an investigational medicinal product
8
9 699 (CTIMP) no formal monitoring and audit was required.
10

11 700

12
13
14 701 *Good Clinical Practice and Ethical Conduct*
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16
17 702 The study will be conducted in accordance with the principles of the research
18
19 703 governance framework operational and good clinical practice in the relevant country.
20

21 704 A favorable ethical opinion has been obtained from the Scotland A REC (Reference
22
23 705 13/SS/0001) and local research and development approval has been obtained prior
24
25 706 to commencement of the study.
26

27
28 707 Local study investigator(s) will be appointed to each site (or for small units, groups of
29
30 708 sites). S/he will be responsible for the overall conduct of the study at the site and
31
32 709 compliance with the protocol and any protocol amendments.
33

34 710

35
36
37 711 **STUDY CONDUCT RESPONSIBILITIES**
38

39 712 *Protocol amendments*
40

41
42 713 Any changes in research activity, except those necessary to remove an apparent,
43
44 714 immediate hazard to the participant in the case of an urgent safety measure, will be
45
46 715 reviewed and approved by the Chief Investigator and Sponsor. Amendments to the
47
48 716 protocol will be submitted in writing to the appropriate REC and local Research and
49
50 717 Development (R&D) department for approval prior to participants being enrolled into
51
52 718 an amended protocol.
53

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3 720 *Protocol violations and deviations*
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5 721 Investigators will not implement any deviation from the protocol without agreement
6
7 722 from the Chief Investigator and appropriate REC and R&D department approval
8
9 723 except where necessary to eliminate an immediate hazard to trial participants. In the
10
11 724 event that an Investigator needs to deviate from the protocol, the nature of and
12
13 725 reasons for the deviation will be recorded. If this necessitates a subsequent protocol
14
15 726 amendment, this will be submitted to the REC, and local R&D department for review
16
17 727 and approval if appropriate.
18
19

20 728 *Serious breach requirements*
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22
23 729 A serious breach is one which is likely to effect to a significant degree (a) the safety
24
25 730 or physical or mental integrity of the participants of the trial; or b) the scientific value
26
27 731 of the trial. If a potential serious breach is identified by the Chief investigator,
28
29 732 Principal Investigator or delegates, the co-sponsors
30
31 733 (accord.seriousbreach@ed.ac.uk) will be notified within 24 hours. It will be the
32
33 734 responsibility of the co-sponsors to assess the impact of the breach on the scientific
34
35 735 value of the trial, to determine whether the incident constitutes a serious breach and,
36
37 736 if so, report it to the REC.
38

39 737 All violations will be assessed by the sponsor(s) to ascertain if they meet the criteria
40
41 738 for a serious breach. If the sponsor(s) deem the incident to be a violation that does
42
43 739 not constitute a serious breach from the protocol when identified, corrective and
44
45 740 preventative actions will be taken where appropriate and they will be recorded in file
46
47 741 notes, held within the TMF and ISF.
48
49

50 742 *Study record retention*
51

52
53 743 All study documentation will be kept for a minimum of 5 years from the protocol
54
55 744 defined end of study point. When the minimum retention period has elapsed, study
56
57 745 documentation will not be destroyed without permission from the sponsor.
58
59
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5 747 *End of study*
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7

8 748 The end of study date was finalised in the protocol after the study commenced; the
9
10 749 agreed end of study date is 31/12/2016. The Investigators and/or the trial steering
11
12 750 committee and/or the co-sponsor(s) have the right at any time to terminate the study
13
14 751 for clinical or administrative reasons.

15
16 752 The end of the study will be reported to the REC within 90 days, or 15 days if the
17
18 753 study is terminated prematurely. The Investigators will inform participants of the
19
20 754 premature study closure and ensure that the appropriate follow up is arranged for all
21
22 755 participants involved. A summary report of the study will be provided to the REC and
23
24 756 Regulatory Authority within 1 year of the end of the study.
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30 758 **REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS**

31
32 759 Ownership of the data arising from this study resides with the study team. On
33
34 760 completion of the study, the study data will be analysed and tabulated, and a clinical
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36 761 study report will be prepared in accordance with good clinical practice guidelines.
37
38 762 The clinical study report will be used as the basis for publication and presentation at
39
40 763 scientific meetings. Investigators have the right to publish orally or in writing the
41
42 764 results of the study. Summaries of results will also be made available to Investigators
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44 765 for dissemination within their clinics (where appropriate and according to their
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46 766 discretion).
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51 768 **DISCUSSION**

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54 769 The data provided by this study will inform the information given to women about
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56 770 reduced fetal movements and their management when they present to maternity
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3 771 services; which has been recurrently identified by Confidential Enquiries into
4
5 772 antepartum stillbirths as suboptimal^{26 27}. Data from the AFFIRM study will be able to
6
7 773 be compared to results from two other active studies which aim to improve mothers
8
9 774 awareness and reporting of reduced fetal movements. My Babies Movement
10
11 775 (ACTRN 12614000291684) is stepped-wedge cluster trial of a mobile phone
12
13 776 application to help women get to know their baby's movements, to be mindful of
14
15 777 movements every day and not to wait to report concerns to their maternity care
16
17 778 provider. The Mindfetalness study (NCT02865759) is a cluster trial of 39,000 women
18
19 779 randomised to routine antenatal care or the Mindfetalness brochure and website.⁴⁵
20
21 780 Women participating in the Mindfetalness process will spend 15 minutes each day
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23 781 getting to know their babies movements and will specifically be encouraged to
24
25 782 contact their health provider if their perceive reduced fetal movements. This primary
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27 783 outcome of this study is an Apgar score <7 at 5 minutes; stillbirth and perinatal
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29 784 deaths will be recorded as tertiary endpoints of this study.⁴⁵ These large studies will
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31 785 provide much needed robust evidence to determine whether increased maternal
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33 786 awareness of reduced fetal movements combined with a standardised management
34
35 787 protocol to identify acute or chronic fetal compromise can reduce stillbirth³².

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40 78841 **PEER REVIEW**

42
43 790 This project has been peer reviewed internally, and was externally peer reviewed
44
45 791 during the process of securing funding from the Chief Scientist's Office of the
46
47 792 Scottish Government, Tommy's and Sands.

48
49
50 79351 **FUNDING**

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53 794
54 795 The AFFIRM study is investigator initiated and funded by Chief Scientist Office,
55
56 796 Scottish Government (CZH/4/882), Tommy's and Sands, the Stillbirth and Neonatal
57
58 797 Death Charity. CJW was supported in this work by NHS Lothian via the Edinburgh
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3 798 Clinical Trials Unit. AEPH is supported by a Clinician Scientist fellowship from the
4
5 799 National Institute for Health Research (NIHR; CS-2013-009). This protocol presents
6
7 800 independent research funded by the National Institute for Health Research (NIHR).
8
9 801 The views expressed are those of the author(s) and not necessarily those of the
10
11 802 NHS, the NIHR or the Department of Health.
12

13 803

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16
17 805 The authors would like to acknowledge the support of Perinatal Ireland and Dr Mary
18
19 806 Higgins (University College Dublin, National Maternity Hospital, Dublin).
20

21 807

22 808 **CONTRIBUTIONS**

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24
25 809 Contributors AEPH, CJW, SJES, CJC, SCB, MRD, SW and JEN were involved in
26
27 810 developing the trial design. AEPH, CJW, SJES, AR and JEN were involved in
28
29 811 drafting and revision of the article. CJW and AR were involved in drafting the
30
31 812 statistical aspects of the protocol. JS provided feedback on behalf of a stakeholder
32
33 813 organisation. AEPH, CJW, SJES, CJC, SCB, JFF, MG, AH, FMM, EM, AR, MRD, JS,
34
35 814 SW and JEN were involved in preparing the overall study design. AEPH, JEN and
36
37 815 MRD prepared education videos for online training. AEPH, SJES, SJS, MG, AH,
38
39 816 FMM and JEN facilitated recruitment of sites. AEPH, CJW, SJES, CJC, SCB, JFF,
40
41 817 MG, AH, FMM, EM, AR, MRD, JS, SW and JEN will be involved in the collection,
42
43 818 management, analysis and interpretation of data and final writing of the trial report.
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46 820 **COMPETING INTERESTS**

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49 821 None declared.
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822 **ABBREVIATIONS**

823	ACCORD	Academic and Clinical Central Office for Research & Development -
824		Joint office for University of Edinburgh and NHS Lothian
825	BMI	Body Mass Index
826	CTG	Cardiotocograph
827	CTIMP	Clinical Trial of an Investigational Medicinal Product
828	ECTU	Edinburgh Clinical Trials Unit
829	FGR	Fetal growth restriction
830	MHRA	Medicines and Healthcare products Regulatory Agency
831	NICE	National Institute for Health and Social Care Excellence
832	NIHR	National Institute for Health Research
833	NIMATS	Northern Ireland Maternity Statistics database
834	NRPS	National Perinatal Reporting System
835	ONS	Office of National Statistics
836	PSANZ	Perinatal Society of Australia and New Zealand
837	RCOG	Royal College of Obstetricians and Gynaecologists
838	R&D	Research and Development
839	REC	Research Ethics Committee
840	RFM	Reduced Fetal Movements
841	SPIMMR	Scottish Perinatal and Infant Mortality and Morbidity Report
842	TMF	Trial Master File
843	TSC	Trial Steering Committee
844	WHO	World Health Organisation
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994 **FIGURE LEGENDS**

995 Figure 1 - Stepped wedge design. The shaded areas (both light and dark) indicate
996 periods in which the interventions are being implemented. The lighter areas indicate
997 the “transition” period during which data will not be collected for the control or
998 intervention group. The order in which hospital groupings implement the interventions
999 will be determined via randomization.

1000 Figure 2 – Flow chart for the management of women presenting with reduced fetal
1001 movements for sites implementing the AFFIRM study. Abbreviations: AC - abdominal
1002 circumference, CTG- cardiotocograph, DVP - deepest vertical pool, EFW - estimated
1003 fetal weight, FGR - fetal growth restriction, LV - liquor volume, RFM - reduced fetal
1004 movement, USS - ultrasound scan.

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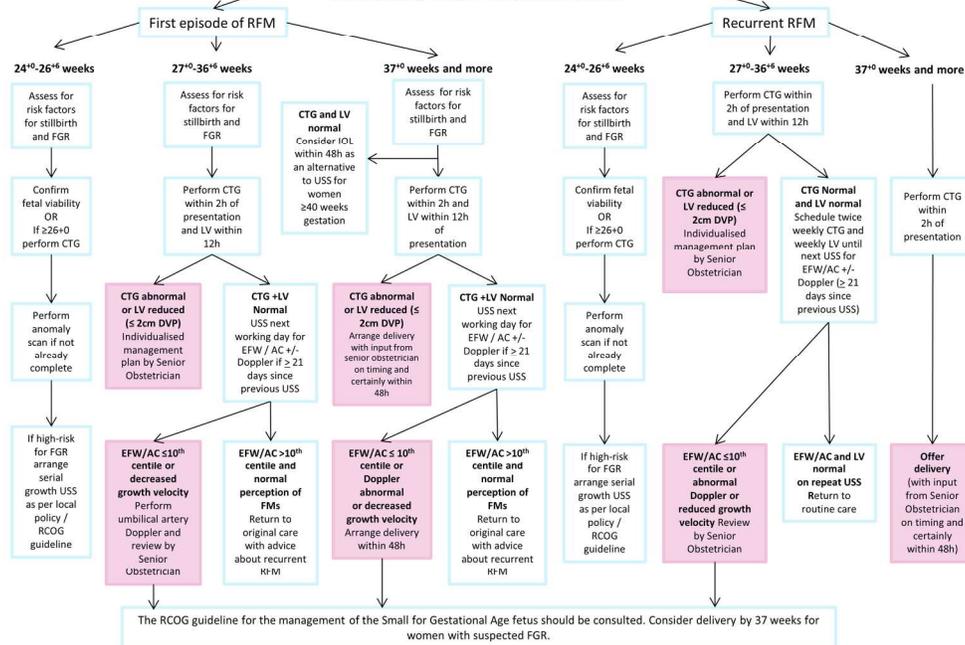
Hospital groupings	Months since Start of Trial								
	1-4	5-8	9-12	13-16	17-20	21-24	25-28	29-32	33-36
1-3		Light	Dark						
4-6			Light	Dark	Dark	Dark	Dark	Dark	Dark
7-9				Light	Dark	Dark	Dark	Dark	Dark
10-12					Light	Dark	Dark	Dark	Dark
13-15						Light	Dark	Dark	Dark
16-18							Light	Dark	Dark
19-21								Light	Dark
22-24									Light

Stepped wedge design. The shaded areas (both light and dark) indicate periods in which the interventions are being implemented. The lighter areas indicate the "transition" period during which data will not be collected for the control or intervention group. The order in which hospital groupings implement the interventions will be determined via randomization.

190x142mm (300 x 300 DPI)

For peer review only

Woman attends with reduced fetal movements



Flow chart for the management of women presenting with reduced fetal movements for sites implementing the AFFIRM study. Abbreviations: AC - abdominal circumference, CTG- cardiotocograph, DVP - deepest vertical pool, EFW - estimated fetal weight, FGR - fetal growth restriction, LV - liquor volume, RFM - reduced fetal movement, USS - ultrasound scan.

190x142mm (300 x 300 DPI)

WHO TO CONTACT IF YOU ARE CONCERNED:
 (space for sticky with local contact information)



APS Group Scotland
 DPPAS33137
 Version 3 March 2015



In touch with **YOUR BABY**

A guide to your baby's
 movements during
 pregnancy



For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

Why are my baby's movements important?

Why are we asking women to get to know their baby's movements?

One of the easiest ways to tell if your baby is healthy is to be aware of how much he or she is moving. Every baby is different and we are asking women to take time to become familiar with their baby's own individual pattern of movements. A reduction or change in **your** baby's movements is what is important.

What can affect my baby's movements?

You are less likely to be aware of your baby's movements when active or busy. Some drugs e.g. strong pain relief or sedatives can get into an unborn baby's circulation and affect the movements. Alcohol and smoking (active and passive smoking) may also affect the baby.

Why are my baby's movements important?

If you notice your baby is moving less than usual, or the pattern of movements has changed, this could be the first sign that your baby may not be well or is not growing properly in the womb. Research has shown that a reduction in the baby's movements may indicate an increased risk of stillbirth. You may hear your midwife or doctor referring to 'reduced fetal movement', or RFM for short.

What are the risks of stillbirth?

Stillbirth affects one in 200 babies after 24 weeks gestation and is one of the most common of the serious complications of pregnancy, affecting the lives of around 4,000 families every year in the UK.

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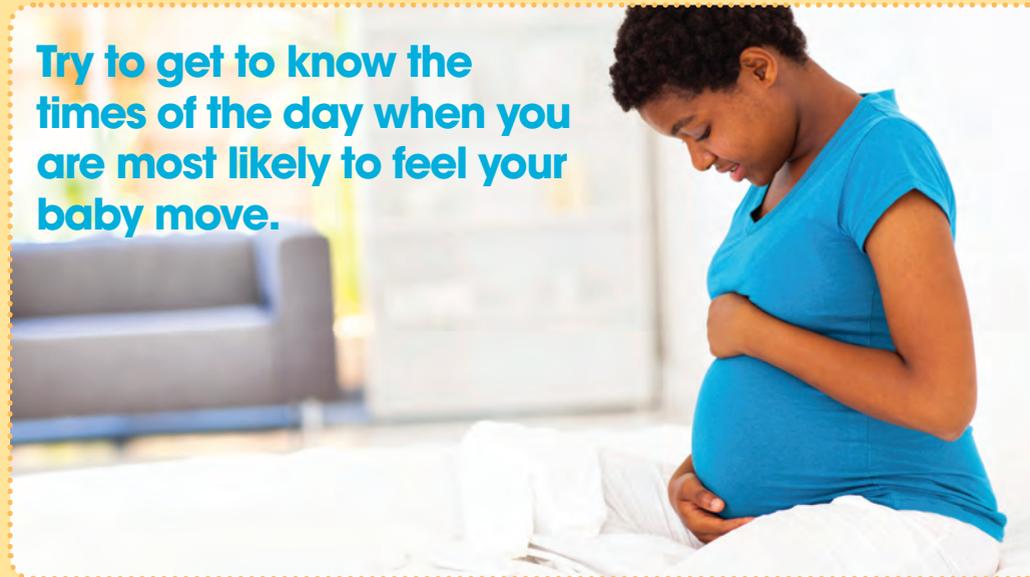
One of the easiest ways to tell if your baby is healthy is to see how much he or she is moving. This booklet tells you what to look out for during your pregnancy.

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Every baby is different. It is good to get to know your baby's own movements and the pattern of their sleeping and waking and report to us if you notice a reduction in these movements.



Try to get to know the times of the day when you are most likely to feel your baby move.



18-24
WEEKS



24-36
WEEKS



Most women begin to feel their baby move between 18-24 weeks. At first it may feel like 'bubbles', 'flutterings' or 'like trapped wind'. These are often very short and stop and start. It might take you a little while to be sure what you are feeling. But you will soon get to know the feelings. If this is your second baby, you will know what to look out for and may recognise your baby moving sooner.

Everyone is different when it comes to their movements. There are many reasons you might not feel movements as early as you expect. This includes your body weight, the position of your baby and the location of your placenta. What is important is your baby is growing well. Your midwife will be able to discuss this with you further at your 22 week check.

You will have your own way of describing your baby's own movements. Women often describe their baby's movements as 'rolling', 'kicking', 'pushing', 'jabs', 'elbowing' and 'stretches'.

Between 24-36 weeks you will start to recognise your baby's movements more quickly and become more used to the feeling. It is usually easier to feel your baby's movements when you are lying down, e.g. at night time. It is harder to feel your baby move when you are on your feet and moving around.

Try to get to know the times of the day you are most likely to feel your baby move. This will help you to know if he or she is moving less than normal or if movements have stopped.

Occasionally your baby will get hiccups. These do not count as movements. If you are unsure what you should expect when your baby hiccups, speak to your midwife.

Appendix 2 - Audit of compliance with AFFIRM protocol

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3 Compliance with the AFFIRM management protocol (the management plan for women presenting with reduced fetal movement) will be determined by to
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5 means:

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8 A) Telephone / email contact with Principal Investigators at each site to determine which aspects of the AFFIRM protocol have been implemented effectively.

9
10 This will involve email contact with Principal Investigators to alert them to the request for information, an email detailing the information required, and then
11
12 a phone call to elicit the information (unless it had already been supplied). Investigators will be asked which of the following elements they had implemented:
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14 issuing leaflets to all pregnant women, cardiotocography within 2 hours of presentation, measurement of amniotic fluid volume within 12 hours of
15
16 presentation, growth scan by the next working day for all women presenting with reduced fetal movement (and who had not had a growth scan within the
17
18 last three weeks, or who were not being induced within 48 hours), and induction of labour within 48 hours for women presenting with recurrent reduced
19
20 fetal movement at or after 37 weeks gestation. "Effective implementation" was defined as the above management for 4/5 of these elements for 80% or more
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22 of the time.
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28 B) An audit to determine whether the perception of the site Principal Investigator is supported by review of actual decision making will be performed for the
29
30 following elements: cardiotocography within 2 hours of presentation, measurement of amniotic fluid volume within 12 hours of presentation, growth scan by
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32 the next working day for all women presenting with reduced fetal movement (and who had not had a growth scan within the last three weeks, or who were
33
34 not being induced within 48 hours), and induction of labour within 48 hours for women presenting with recurrent reduced fetal movement at or after 37
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36 weeks gestation.
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40 This will be conducted by asking sites to complete an audit of the management of all women presenting with reduced fetal movement over the course of one
41
42 calendar month. Sites will be asked to complete an audit form for each participant. The audit form template (see below) has been generated by the central
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1 AFFIRM study team; anonymized forms will be analysed centrally. There will not be an attempt to corroborate Principal Investigator perception of the
2
3 proportion of women who were given leaflets, nor will there be any attempt to incorporate the proportion of staff who had completed the e-learning
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5 package into analysis of whether any specific site has implemented the intervention or not.
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For peer review only

Compliance with AFFIRM reduced fetal movements protocol, One month data collection AUDIT [Month & Year] Unit name: [Name of Hospital]

If you assess a woman with reduced fetal movements (RFM), please complete the questions below. Do not worry if the woman has been seen in other areas of the hospital by other staff, we would rather have multiple reports for the same woman than miss episodes of RFM.

INSERT Patient Sticker (or WRITE name and CHI /NHS number)				AREA WHERE SEEN (CIRCLE) Triage / Labour ward / Day Assessment Unit (DAU) Other (specify area i.e. antenatal ward): _____					
Date and time of presentation with reduced fetal movements.	DATE: ____/____/____ TIME ____:____ am / pm			GESTATION AND EDD:	_____ WEEKS _____ DAYS EDD: _____				
Referred by (TICK BOX):	Self	Community Midwife	GP	ANC	Triage	DAU	Other (specify: _____)		
What was the primary reason for attending/phoning? (TICK BOX):	Reduced Fetal Movements			Other (specify: _____)					
How many times has the woman attended before this visit, with RFM? (TICK BOX):	None – first attendance	Once previously	Unknown	Multiple times (please provide the gestation at each presentation i.e. 30+6)	1	2	3	4	5
What was the time interval from the woman first being aware of reduced fetal movements and attending the hospital (in hours)?					HOURS: _____				
Has she been given a leaflet “Your baby’s movements in pregnancy”? (TICK BOX):	Yes – she already has one	Yes – I have given one to her today		Locally Created Leaflet Given	NO				
Has this woman had a growth USS in this pregnancy? (TICK BOX):	No, she has not had a growth scan	Yes, within the last 3 weeks (date of scan): DATE: ____/____/____		Yes, but more than 3 weeks ago (date of scan): DATE: ____/____/____					

CONTINUATION: NHS/ CHI NUMBER:

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Are any of the following risk factors for Fetal growth restriction present (CIRCLE all that apply)?

Age ≥40 or ≤16	Smoker ≥20cpd	Known or suspected growth restriction	Congenital anomaly	Raised BP (essential hypertension, pre-eclampsia or pregnancy induced hypertension)	Previous pre-eclampsia	Diabetes or gestational diabetes	Previous FGR or stillbirth
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What investigations were conducted during this episode of reduced fetal movement?

Please record below the date and time that these investigations were completed or indicate if not performed.			Please provide the results (CIRCLE):
CTG	Not performed <input type="checkbox"/>	DATE: ___/___/___ TIME: ___:___ am/pm <u>Computerised CTG</u> : YES / NO (CIRCLE)	Normal / Suspicious / Pathological
Liquor volume assessment on scan	Not performed <input type="checkbox"/>	DATE: ___/___/___ TIME: ___:___ am/pm	Normal / Reduced / Increased
Growth scan	Not performed <input type="checkbox"/>	DATE: ___/___/___ TIME: ___:___ am/pm	Normal / EFW < 10 th centile/ AC < 10 th centile / EFW and AC < 10 th centile
Umbilical Artery Doppler	Not performed <input type="checkbox"/>	DATE: ___/___/___ TIME: ___:___ am/pm	Normal/.> 95 th centile/absent EDF/reversed EDF
MCA Doppler	Not performed <input type="checkbox"/>	DATE: ___/___/___ TIME: ___:___ am/pm	Normal/<5 th centile

DELIVERY METHOD (If available)

Was the woman offered induction of labour	YES / NO (CIRCLE) IF Yes, please provide date, time and method of the induction:	DATE: ___/___/___ TIME: ___:___ am/pm	
Was the woman offered elective caesarean section as a result of the reduced fetal movement?	YES / NO (CIRCLE) IF Yes, please provide date, time and reason:	DATE: ___/___/___ TIME: ___:___ am/pm	Please provide the reason for the elective Caesarean section:



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___ Page 1 ___
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___ Page 4 ___
	2b	All items from the World Health Organization Trial Registration Data Set	_Included throughout protocol_
Protocol version	3	Date and version identifier	___ Page 4 ___
Funding	4	Sources and types of financial, material, and other support	___ Page 28 ___
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_Names and affiliations Page 1 and 2; Contributions Page 28_
	5b	Name and contact information for the trial sponsor	___ Page 24 ___
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_Not applicable_

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3		5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
4			___Page 24___
5			
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7			
8	Introduction		
9			
10	Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
11			__Pages 5-11__
12		6b	Explanation for choice of comparators
13			__Pages 8-9__
14	Objectives	7	Specific objectives or hypotheses
15			__Pages 11-12__
16	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
17			__Pages 13- 14 and Figure 1__
18			
19			
20	Methods: Participants, interventions, and outcomes		
21			
22	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
23			__Pages 13 & 16__
24			
25	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
26			__Pages 14-15__
27			
28	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
29			__Pages 17-18 and Figure 2__
30		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
31			__Not applicable in AFFIRM trial__
32		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
33			__Pages 17-18__
34		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
35			__Not applicable__
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3	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	__Pages 12-13__
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8	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	__Randomisation by site explained in Figure 1 and Pages 13-14__
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14	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	__Pages 21-22__
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17	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	__Page 22__
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20	Methods: Assignment of interventions (for controlled trials)			
21	Allocation:			
22				
23	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	__Page 17__
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29	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	__Page 17__
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33	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	__Page 17__
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36	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	__Page 17__
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39		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_ Not applicable in AFFIRM study__
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49**Methods: Data collection, management, and analysis**

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	__Pages 18-21__
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	__Not applicable__
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	__Pages 19-20__
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	__Pages 22-23__
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	__Page 23__
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	__Pages 22-23__

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_DMC not required, explanation Pg 24__
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	__Pages 18, 25-26__
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	__Page 24__
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	__Page 13__

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3 **Ethics and dissemination**
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5 Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	__Page 25__
8 Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	__Page 25__
12 Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	__Page 25__
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	__Not applicable__
19 Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	__Page 20__
22 Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	__Page 29__
25 Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	__Page 27__
28 Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	__Page 24__
31 Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	__Page 27__
	31b	Authorship eligibility guidelines and any intended use of professional writers	__Page 28__
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	__Not applicable__

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40 **Appendices**
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Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_Not Applicable__
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_Not Applicable__

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.

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BMJ Open

Can Promoting Awareness of Fetal movements and Focussing Interventions Reduce Fetal Mortality? - A stepped wedge cluster randomised trial (AFFIRM)

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-014813.R3
Article Type:	Protocol
Date Submitted by the Author:	02-Mar-2017
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Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Research methods
Keywords:	Reduced Fetal Movements, Perinatal Mortality, Stillbirth, Neonatal Death, Fetal Growth Restriction

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3 **1 Study Protocol**
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5 2 Can Promoting Awareness of Fetal movements and Focussing Interventions Reduce
6
7 3 Fetal Mortality? - A stepped wedge cluster randomised trial (AFFIRM)
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3 40 **Abstract**
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5 41 *Background* - In 2013, the stillbirth rate in the UK was 4.2 per 1,000 live births,
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7 42 ranking 24th out of 49 high-income countries, with an annual rate of reduction of only
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9 43 1.4% per year. The majority of stillbirths occur in normally formed infants, with
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11 44 (retrospective) evidence of placental insufficiency the commonest clinical finding.
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13 45 Maternal perception of reduced fetal movements (RFM) is associated with placental
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15 46 insufficiency and increased risk of subsequent stillbirth.
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18 47 This study will test the hypothesis that the introduction of a package of care to
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20 48 increase women's awareness of the need for prompt reporting of RFM and
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22 49 standardised management to identify fetal compromise with timely delivery in
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24 50 confirmed cases, will reduce the rate of stillbirth. Following the introduction of a
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26 51 similar intervention in Norway the odds of stillbirth fell by 30%, but the efficacy of this
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28 52 intervention (and possible adverse effects and implications for service delivery) have
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30 53 not been tested in a randomised trial.
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33 54 *Methods* - We describe a stepped wedge cluster trial design, in which participating
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35 55 hospitals in the UK and Ireland will be randomized to the timing of introduction of the
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37 56 care package. Outcomes (including the primary outcome of stillbirth) will be derived
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39 57 from detailed routinely collected maternity data, allowing us to robustly test our
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41 58 hypothesis. The degree of implementation of the intervention will be assessed in
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43 59 each site. A nested qualitative study will examine the acceptability of the intervention
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45 60 to women and health care providers and identify process issues including barriers to
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47 61 implementation.
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50 62 *Ethics and Dissemination* – Ethical approval was obtained from the Scotland A
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52 63 Research Ethics Committee (Ref 13/SS/0001) and from Research and Development
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54 64 offices in participating maternity units. The study started in February 2014 and
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56 65 delivery of the intervention completed in December 2016. Results of the study will be
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3 66 submitted for publication in peer-reviewed journals and disseminated to local
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5 67 investigating sites to inform education and care of women presenting with RFM.
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8 68 *Trial Registration*

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10 69 www.clinicaltrials.gov NCT01777022
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12 70 *Version*

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15 71 Protocol Version 4.2, 3rd February 2017
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17 72 *Keywords*

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20 73 Reduced Fetal Movements; Perinatal Mortality; Stillbirth; Neonatal Death; Fetal
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22 74 Growth Restriction.
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27 76 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

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29 77 • This trial directly addresses the need for studies of the information given to
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31 78 women regarding fetal movements and the subsequent management of reduced
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33 79 fetal movements identified by Confidential Enquiries into Antepartum Stillbirths,
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35 80 Systematic Reviews and the Stillbirth Priority Setting Partnership.

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37 81 • A stepped-wedge cluster trial design in combination with routinely collected
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39 82 maternity data allows the trial to be adequately powered to detect a difference in
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41 83 stillbirth as a primary outcome.

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43 84 • The pragmatic nature of the study represents the potential impact of the
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45 85 introduction of such standardised care into clinical practice.

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47 86 • The nested qualitative study will provide information regarding the acceptability
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49 87 of the intervention and identify barriers and facilitators to its adoption.

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51 88 • The lack of information on resource use before and throughout the study period
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53 89 limits the ability to understand the consequences of the intervention on maternity
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55 90 unit workload.
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3 93 **INTRODUCTION**
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5 94 *Stillbirth*
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8 95 Stillbirth, defined in the UK as a baby with no signs of life after 24 weeks of completed
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10 96 pregnancy ¹, remains the major cause of perinatal mortality in high-income
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12 97 environments, with a recent series of papers in the Lancet on stillbirth issue calling for
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14 98 renewed action in this area ². There is no single “cause” of stillbirth, and a significant
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16 99 proportion of stillbirths remain unexplained, but fetal growth restriction, maternal
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18 100 hypertension and low socioeconomic status are amongst the identifiable risk factors ³.
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20 101 The concept that more can be done to reduce stillbirth in the UK and Ireland is
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22 102 supported by data showing a marked variation in rates between resource rich
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24 103 countries, when similar definitions of stillbirth are used ². Notably, the UK has a higher
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26 104 rate than comparable resource rich countries such as Germany, Netherlands, New
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28 105 Zealand and Norway with rates in the UK some 50% greater than those of the
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30 106 Netherlands. Disappointingly, the annual rate of reduction in stillbirth from 2000 to
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32 107 2014 in the UK was only 1.4% compared to 6.8% in the Netherlands and 2.8% in New
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34 108 Zealand ². Rates of stillbirth in Scotland (3.7 per 1,000 births in 2014) and Ireland, at
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36 109 (4.4 per 1,000 livebirths in 2013) are similar to rates in England and Wales at 4.2 per
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38 110 1,000 livebirths (England and Wales, 2014) ⁴. The reduction of avoidable harm for
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40 111 women and babies is viewed as a major priority for Government and its agencies
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42 112 throughout the UK and Ireland. Consequently, several initiatives have been
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44 113 developed by national governments in the UK and Ireland including the Scottish
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46 114 Government Stillbirth Working Group, NHS England Saving Babies’ Lives Care
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48 115 Bundle and the Welsh Assembly 1000 Lives Plus strategy. These strategies have
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50 116 identified the need for better evidence to guide efforts to prevent stillbirths.
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53 117 Using a robust priority setting strategy ⁵ the Lancet Stillbirth’s series steering
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55 118 committee identified issues around detection and management of reduced fetal
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57 119 movements (RFM) amongst the top ten key research questions on prevention and
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3 120 management of stillbirth⁶. This was confirmed in the UK-based Stillbirth Priority
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5 121 Setting partnership involving over 1,700 parents and professionals which identified
6
7 122 two relevant issues among the highest ranked research questions regarding stillbirth:
8
9 123 i) which investigations identify a fetus at risk of stillbirth after a mother believes she
10
11 124 has experienced reduced fetal movements? and ii) would more accessible evidence-
12
13 125 based information on signs and symptoms of stillbirth risk, designed to empower
14
15 126 women to raise concerns with healthcare professionals, reduce the incidence of
16
17 127 stillbirth?⁷ Thus, RFM has been identified as a highly-relevant area of study by
18
19 128 parents, professionals and researchers.
20
21 129

22 23 130 *Reduced Fetal Movements, Stillbirth and Placental Insufficiency*

24
25
26 131 There is a clear association between maternal perception of RFM and late stillbirth
27
28 132 dating back over four decades⁸. In a recent series of 2,000 women, the adjusted OR
29
30 133 (95% CI) of late stillbirth in women with RFM (compared with controls) was 2.37
31
32 134 (1.29-4.35)⁹. One international study of 1,714 women who experienced a stillbirth
33
34 135 found that 30% had noted significant RFM prior to the diagnosis of stillbirth¹⁰.
35
36 136 Although the mechanisms have not been fully delineated, it is likely that RFM and
37
38 137 stillbirth are linked by a common pathology, that of placental dysfunction¹¹. There is
39
40 138 good evidence linking placental dysfunction and RFM. Compared to controls with an
41
42 139 active fetus women who have fewer fetal movements on ultrasound scan immediately
43
44 140 prior to caesarean section are more likely to have umbilical cord gas measurements
45
46 141 indicative of acidaemia, hypoxaemia, and hypercapnia¹². Women delivering within
47
48 142 one week of an episode of RFM show differences in placental structure and function
49
50 143 which are reminiscent of those seen in fetal growth restriction (FGR) and stillbirth^{13 14}.
51
52 144 Additionally, the odds of fetal growth restriction (FGR, defined as being at less than
53
54 145 the 10th centile for gestation adjusted birthweight) were greater in women with RFM
55
56 146 compared with controls (adjusted OR 1.6, 95% CI 1.1–2.2¹⁵). Taken together these
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3 147 data are strong evidence that placental dysfunction is associated with RFM, and a
4
5 148 causative pathway seems likely.

6
7 149 The evidence linking placental dysfunction and stillbirth is even stronger; a systematic
8
9 150 review of placental pathology in stillbirths described abnormalities in up to 65% of
10
11 151 cases¹⁰. Amongst the 291 stillbirths in Scotland in 2010, 137 (47%) had evidence of
12
13 152 placental dysfunction¹⁶. Given that the placenta was examined in only 80% of
14
15 153 stillbirths, the true prevalence of placental dysfunction is likely to be higher. In
16
17 154 addition, between 20%-40% of stillborn babies are reported to have FGR, as defined
18
19 155 by a birthweight less than the 10th centile¹⁷. Additionally, the Lancet report notes that
20
21 156 “placental pathologies accounted for one in four deaths across all gestational ages,
22
23 157 and were contributory or causal in more than half of cases”⁶. Given that stillbirth is
24
25 158 strongly related to placental dysfunction, and RFM is a “biomarker” of placental
26
27 159 dysfunction then better management of women presenting with RFM focussing on the
28
29 160 detection of placental dysfunction might reduce the risk of stillbirth.
30

31
32 161

33 162 *Formal Fetal Movement Counting*

34
35 163 Although prenatal detection of FGR is improved by fetal movement counting¹⁸, a
36
37 164 systematic review¹⁹, and a large and influential cluster randomised trial (which
38
39 165 dominates the systematic review) showed that routine fetal movement counting using
40
41 166 the count to ten charts had no effect on perinatal mortality²⁰. Thus, the National
42
43 167 Institute for Health and Social Care Excellence (NICE) recommended that “Routine
44
45 168 formal fetal movement counting should not be offered”²¹. Importantly, the large
46
47 169 cluster randomised trial tested a specific alarm limit for RFM, but did not recommend
48
49 170 a specific management strategy for women who did present with RFM. There were
50
51 171 two important observations from this study, firstly that in both groups the perinatal
52
53 172 mortality rate was lower than contemporary or subsequent periods in the UK and
54
55 173 secondly that more women in the fetal movement counting arm came in with a live
56
57 174 baby who subsequently died compared with the control arm (19 vs 11), suggesting
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1
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3 175 that one reason the strategy failed to reduce perinatal mortality was inadequate
4
5 176 investigation and management of those presenting with RFM ²⁰.

6
7 177

8
9 178 *Optimal strategy for determining RFM to prompt maternal presentation to the*
10
11 179 *maternity service*

12
13 180 Maternal concern about RFM is a common reason to contact maternity services with
14
15 181 between 6-15% of women presenting during the third trimester.^{22 23} Nevertheless,
16
17 182 delays in reporting RFM to maternity care providers may increase the risk of adverse
18
19 183 outcome.^{24 25} The lack of good-quality information given to women about fetal
20
21 184 movements has been highlighted as an example of suboptimal care in Confidential
22
23 185 Enquiries into Antepartum Stillbirth.^{26 27} Qualitative studies suggest that women
24
25 186 frequently perceive RFM two days prior to the diagnosis of fetal death, and in some
26
27 187 cases contractions were misinterpreted as fetal movements.²⁸ Therefore, giving
28
29 188 information to women regarding fetal movements and when they should be
30
31 189 concerned about RFM is a key component of an intervention to reduce stillbirth.

32
33 190 However, giving clear information about RFM can be challenging as there is no
34
35 191 uniform threshold of fetal movements below which perinatal morbidity increases ²³,
36
37 192 and no evidence that a specific threshold performs better than maternal perception of
38
39 193 reduced fetal movements alone ⁸. Current guidelines from the RCOG and PSANZ ²⁹
40
41 194 ³⁰, informed by a large Norwegian study ³¹ suggest that it is *maternal perception* of
42
43 195 decreased fetal movement which is important. Therefore, information for pregnant
44
45 196 women in this study (shown in Supplementary File 1) described the importance of
46
47 197 fetal movements, the need to get to know normal fetal activity, how fetal movements
48
49 198 change in late pregnancy and who to contact if the mother perceives RFM. The
50
51 199 educational package aimed to ensure that these messages were reinforced by staff
52
53 200 behaviour at antenatal contacts.

54
55
56 201

57
58 202 *Optimal strategy for investigation and management of women presenting with RFM.*
59
60

1
2
3 203 A recent systematic review found there are no proven strategies for the investigation
4
5 204 and management of women presenting with RFM ³². Cardiotocography (CTG) is
6
7 205 routinely used to ascertain fetal wellbeing, and it is the cornerstone of the RCOG
8
9 206 guideline ³⁰. However, data from Norway, suggests that ultrasound assessment of
10
11 207 fetal size is often the most helpful investigation, performing well on both an absolute
12
13 208 basis, and compared with other interventions ³³. In a series of over 3,000 women with
14
15 209 RFM, ultrasound (including measurement of fetal biometry and liquor volume) was
16
17 210 found to be useful in detecting abnormalities in 11.6% of scans. In 71% of women in
18
19 211 whom an abnormality was found, ultrasound was the only technique that detected an
20
21 212 abnormality. Additionally, 85% of abnormalities detected by ultrasound, were
22
23 213 important in informing the clinical management of the woman ³³. These data are
24
25 214 supported by a smaller UK study which found that abnormalities detected on CTG or
26
27 215 ultrasound scan were most strongly associated with adverse outcome in women with
28
29 216 RFM, with identification of abnormal estimated fetal growth centile on scan being the
30
31 217 test most highly predictive of poor outcome ³⁴. Perhaps this is not surprising, given the
32
33 218 strong association between RFM and placental dysfunction and the central
34
35 219 importance of ultrasound in the identification and management of small for gestational
36
37 220 age babies ³⁵. Given these data, it is concerning that a survey of clinicians in Scotland
38
39 221 showed that fewer than 5% would routinely refer women with RFM for ultrasound
40
41 222 examination (unpublished data from June 2012), and a survey of 223 UK midwives
42
43 223 and obstetricians described that 17.9% of respondents would perform an ultrasound
44
45 224 scan ³⁶. These views of clinicians may reflect the variable quality of local guidelines,
46
47 225 which are frequently not based on national recommendations, even those for which
48
49 226 there is strong evidence ³⁷. The variation in information given to women and
50
51 227 subsequent management of RFM has been highlighted as sources of suboptimal care
52
53 228 in two confidential enquiries into antepartum stillbirth ^{26 27}. Therefore, we believe that
54
55 229 current investigation of women presenting with RFM is inadequate, hence using the
56
57 230 best available evidence, we have drafted what we consider to be a robust evaluation
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1
2
3 231 protocol for investigation of women with RFM.
4
5 232
6
7 233 *Potentially efficacy of a package of intervention for RFM*
8
9 234 Supportive data for the package of interventions used in this study (information for
10
11 235 women and standardised management protocol) comes from a large observational
12
13 236 “clinical quality improvement study” in Norway which found a significant fall in rates of
14
15 237 stillbirth (from 3.0/1,000 to 2.0/1,000 [OR 0.67 95% CI 0.48–0.93]) after the
16
17 238 introduction of an intervention package consisting of written information for women
18
19 239 about awareness of RFM combined with consensus guidelines for health
20
21 240 professionals about their management ³¹. Although this study was not randomised,
22
23 241 and therefore constitutes only level II-3 evidence, it has informed recommendations
24
25 242 from the Royal College of Obstetricians and Gynaecologists (RCOG) and Perinatal
26
27 243 Society of Australia and New Zealand (PSANZ) that “women should be advised to be
28
29 244 aware of their baby’s individual pattern of movements and that if they are concerned
30
31 245 about a reduction in or cessation of fetal movementsthey should contact their
32
33 246 maternity unit” ^{29 30}. Following initial publication of the Norwegian study, a re-analysis
34
35 247 was required as discrepancies between stillbirth rates in the study and the Medical
36
37 248 Birth Registry of Norway were identified. This reanalysis found the reduction in
38
39 249 stillbirth rates was of borderline statistical significance (OR 0.72, 95% CI 0.50-1.03).
40
41 250 The authors concluded that further studies were needed to determine whether this
42
43 251 approach was associated with a reduction in stillbirth ³⁸.
44
45 252 Importantly, in the Norwegian study, there was no increase in the proportion of
46
47 253 women who presented with RFM when rates were compared before and after the
48
49 254 intervention ³¹. However, women with RFM presented significantly earlier to hospital
50
51 255 than they had hitherto, potentially allowing time for intervention to reduce perinatal
52
53 256 mortality. These data suggest that a package of interventions encouraging women
54
55 257 with RFM to present early to hospital, combined with a structured approach to their
56
57 258 management might reduce rates of stillbirth without contributing to a large increase in
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3 259 admissions antenatally.
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6
7 261 *Potential harms of a package of care around increased awareness and optimised*

8
9 262 *management of RFM*

10
11 263 Any clinical intervention which aims to improve outcomes also has the ability to do

12 264 harm. Thus, it is essential that the intervention proposed is rigorously evaluated using

13 265 the gold standard technique of a randomised trial, rather than being introduced as a

14 266 service development. When the study began, there was a small window of

15 267 opportunity to do this, as the enthusiasm to improve current management of RFM is

16 268 such that routine introduction of the package of care is unlikely to be delayed much

17 269 further than the current scheduled end date of this study. Possible harms of a

18 270 package of care consisting of a management plan for identification and delivery of the

19 271 “at risk” fetus, together with strategies for increasing pregnant women’s awareness of

20 272 the need to report early include increased maternal anxiety and increased

21 273 intervention (including hospital admission, induction of labour and Caesarean section)

22 274 which itself is associated with pregnancy related complications. The available

23 275 evidence is reassuring on some of these issues. A systematic review of 23

24 276 publications from 16 studies found three studies involving 2,030 women addressing

25 277 maternal concern and an additional three studies involving 1,468 women investigating

26 278 maternal-fetal attachment. These demonstrated no evidence of increased maternal

27 279 anxiety and results regarding maternal-fetal attachment were discordant.³⁹ In the

28 280 Norwegian service development study, the package of care increased rates of follow

29 281 up of women, but there was no increase in admissions overall, admissions for

30 282 induction or admissions for emergency caesarean section ³¹ – again, whilst

31 283 reassuring these outcomes require formal evaluation in a randomised and relevant

32 284 setting to the UK and Republic of Ireland. The final possible harm of the package is

33 285 around increased resource use, and the opportunity cost of focussing on RFM rather

1
2
3 286 than other potential methods to prevent stillbirth.
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8 288 **RATIONALE**

9
10 289 The aim of this study is to test the hypothesis that a package of interventions
11
12 290 consisting of strategies for increasing pregnant women's awareness of the need to
13
14 291 report early when they perceive a reduction in fetal movements, followed with a
15
16 292 management plan for identification and delivery of the "at risk" fetus in such women,
17
18 293 will reduce rates of stillbirth.
19

20
21 294

22
23 295 **STUDY OBJECTIVES**

24
25
26 296 *Primary Objective*

27
28 297 The primary objective is to answer the research question 'Does the introduction of a
29
30 298 protocol for detection and management of decreased fetal movements reduce rates
31
32 299 of stillbirth?' The secondary objectives are to answer the following research
33
34 300 questions:

- 35
36
37 301 • What is the effect of the intervention on rates of caesarean section and induction
38
39 302 of labour?
40
41 303 • What is the effect of the intervention on rates of admission to the neonatal
42
43 304 intensive care unit?
44
45 305 • What is the effect of the intervention on the proportion of women with FGR
46
47 306 remaining undelivered by 40 weeks gestation?
48
49 307 • What is the acceptability of such a package of care to pregnant women and their
50
51 308 health care providers?
52
53 309 • What other process outcomes are influenced by the intervention, such as health
54
55 310 care provider/patient interactions?
56
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4

5 312 **ENDPOINTS**
6

7
8 313 *Primary Outcome*
9

10 314 The primary endpoint is stillbirth (antepartum and intrapartum). We will use the UK
11 definition of stillbirth which is “a baby delivered without signs of life after 23⁺⁶ weeks”
12

13 315
14 316 ⁴. Where gestation is uncertain we will include all babies with a birth weight of 500g
15 or more.
16 317

17
18
19 318 *Secondary Endpoints*
20

21 319 Other measures of perinatal mortality including:
22

23
24 320 • Stillbirth at 37 weeks gestation and above
25

26
27 321 • Stillbirth at 28 weeks gestation and above (WHO definition of stillbirth)
28

29 322 • Stillbirth at 22 weeks gestation and above (international stillbirth alliance
30 definition)
31 323

32
33 324 • Stillbirths amongst normally formed infants of 22 weeks gestation and above,
34 24 weeks gestation and above, 28 weeks gestation and above and 37 weeks
35 325 gestation and above.
36 326

37
38 327 • Perinatal mortality (defined as stillbirth at 24 weeks gestation and above and
39 deaths in the first seven days of life)
40 328

41
42 329 • Rates of caesarean section
43

44
45 330 • Rates of induction of labour (for any indication)
46

47
48 331 • Rates of elective delivery (induction of labour and caesarean section prior to
49 the onset of labour) overall
50 332

51
52 333 • Rates of induction of labour at 39 weeks gestation or later
53

54
55 334 • Mean gestation at induction of labour
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3 335 • Rates of admission to the neonatal unit (and their reasons)
4
5 336 • Rates of admission to the neonatal unit for more than 48 hours
6
7
8 337 • Rates of admission to the neonatal unit for term babies (those born at 37
9 weeks 0 days or greater)
10 338
11
12 339 • Proportion of infants with fetal growth restriction (less than the 5th centile,
13 customised for gender) remaining undelivered at or after 40 weeks gestation
14 340
15
16 341 • Birthweight centile (according to the Intergrowth birthweight centile calculator
17 at <https://intergrowth21.tghn.org>)
18 342
19
20 343 • Rates of spontaneous vaginal delivery
21
22
23 344 Other secondary outcomes are the baby parameters:
24
25
26 345 • Gestation at birth
27
28
29 346 • Proportion of babies born preterm (<37 weeks gestation)
30
31
32 347 • Gender of the baby
33
34
35 348 • Birthweight of the baby
36
37
38 349 • Apgar score at 5 minutes
39
40 350 • Proportion of babies with 5 minute Apgar score < 7
41
42 351 • Proportion of babies with 5 minute Apgar score < 4
43
44
45 352 • Resuscitation required at birth
46
47

48 353 We will also collect the following data: maternal age, maternity unit of delivery,
49 354 birthweight, gestation of delivery, parity, gestation, sex, smoking (current and ever),
50 355 maternal body mass index (BMI), number of babies (one or more), ethnicity (to allow
51 356 a customised birthweight centile to be generated), method of delivery, deprivation
52 357 category (where available) and other neonatal variables including Apgar score and
53 358 encephalopathy. Adjustment will be made for the following variables: (maternal age,
54
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3 359 maternity unit of delivery, parity, smoking status, maternal BMI, number of babies
4
5 360 [one or more] and ethnicity)

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9
10 362 **STUDY DESIGN**

11
12 363 This is a multicentre, stepped wedge cluster randomised trial of a package of care
13
14 364 consisting of a management plan for identification and delivery of the 'at risk' fetus,
15
16 365 together with strategies for increasing pregnant women's awareness of the need to
17
18 366 report RFM early. The trial developed from a planned quality improvement project
19
20 367 proposed by the Scottish Government to reduce stillbirths. This was planned to
21
22 368 emphasise the importance of fetal movement monitoring and was to be rolled out to
23
24 369 all NHS maternity units in Scotland. However, prior to this change it was agreed that
25
26 370 the roll out could be performed in such a way as to allow the assessment of the effect
27
28 371 of the intervention, the stepped-wedge design would be the natural choice in this
29
30 372 circumstance.

31
32
33 373 The study will take place in participating hospitals in the UK and Ireland (a complete
34
35 374 list is available <http://www.crh.ed.ac.uk/affirm/randomised-hospitals/>). A nested
36
37 375 qualitative study will examine the acceptability of the intervention to patients and
38
39 376 health care providers and identify process issues (barriers to implementation).
40
41 377 Clinical audit (detailed in Appendix 3) conducted after the change in practice will be
42
43 378 used to determine the effect of interventions on process outcomes (e.g. number of
44
45 379 women presenting with reduced fetal movements, interval between perceiving
46
47 380 reduced fetal movements and presentation to hospital, number of ultrasound scans,
48
49 381 number of admissions for induction of labour). A diagram indicating randomisation of
50
51 382 hospital groupings in the stepped wedge design is shown in Figure 1.

52
53
54 383 The interventions will be introduced over a 32 month period. Data will be collected
55
56 384 over a 36 month period. Data in the 'active phase' after introduction of the
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3 385 intervention will be compared to data in the ‘control phase’ – the period during which
4
5 386 usual care processes in study sites are followed from study start to the time of
6
7 387 introduction of the intervention. Given that it will take individual units some time (a) to
8
9 388 effect change in management in their unit from time of introduction of the intervention
10
11 389 and (b) that it will take some time for this change in practice to impact on clinical
12
13 390 outcomes, we plan a “washout” period of two months after the introduction of the
14
15 391 intervention during which data will not be included in either group for analysis (Figure
16
17 392 1). Data will be collected four months after the last birth, a further two months has
18
19 393 been included for data analysis, giving a total study duration of 42 months.
20
21
22 394

23 24 395 **STUDY POPULATION**

25 26 27 396 *Number of participants*

28
29 397 Participants will be those delivering at all the sites over the study period (36 months).
30
31 398 All eligible women will be recruited to the cluster randomised controlled trial. Based
32
33 399 on previous delivery numbers, after accounting for a washout period of two months
34
35 400 (and assuming no withdrawals or losses to follow up) this is estimated to be a total of
36
37 401 around 143,140 women per annum. A subset of around 30 participating women and
38
39 402 30 midwives, sonographers and obstetricians will be recruited to the nested
40
41 403 qualitative study, which is based in the Scottish sites.
42
43

44 404 *Inclusion criteria*

45
46 405 We will include all women delivering at one of the participating maternity units for the
47
48 406 duration of the study. Women who have been seen at any of the maternity units but
49
50 407 who deliver at home will not be included. The duration of the study will be 42 months
51
52 408 from the start of the trial (01/02/2014). For practical reasons, participants for the
53
54 409 nested qualitative study will be recruited from the participating units in Scotland.
55
56

57 410 *Exclusion criteria*

1
2
3 411 We will exclude women as follows:
4

5 412 • Women for whom data on delivery outcomes is still unavailable four months after
6
7 413 the date of delivery
8

9
10 414 • Women delivering in the “washout” period in each unit.
11

12 415 Members of the trial management group and participants who do not
13 416 speak/understand English will be excluded from participating in the nested qualitative
14
15 417 study.
16

17
18
19 418 *Identifying participants*
20

21 419 Women will be identified from those whose data is included in routine data returns
22
23 420 from each unit. Potential participants for the nested qualitative study will be identified
24
25 421 from those attending antenatal clinics in participating hospitals, and/or local staff.
26
27

28 422 *Consenting participants*
29

30
31 423 The main study is a stepped wedge cluster randomised trial of a package of care
32
33 424 which would be introduced in many of the participating units regardless of whether
34
35 425 the trial was on-going or not and the trial uses only routinely collected data on
36
37 426 participants. The ethics committee indicated that formal individual patient consent is
38
39 427 not necessary for the main trial. Participants in the nested qualitative study will be
40
41 428 asked for individual consent.
42

43 429 *Screening for eligibility*
44

45
46 430 As participants are not directly recruited we will not perform any specific screening
47
48 431 tests for this aspect of this project. Participants for the nested qualitative study will
49
50 432 be: (i) Pregnant women attending hospitals who are participating in the main trial in
51
52 433 Scotland. Purposive sampling will ensure that the final sample set includes women
53
54 434 who have and who have not experienced RFM, both before and after the introduction
55
56 435 of the intervention; (ii) Hospital staff (including midwives, ultrasonographers and
57
58
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1
2
3 436 obstetricians/radiologists) working in participating hospitals in Scotland. There will be
4
5 437 no specific screening tests for eligibility for the nested qualitative study, except that
6
7 438 women who have experienced a stillbirth in the index pregnancy will not be
8
9 439 approached.

10
11 440 *Ineligible and non-recruited participants*

12
13
14 441 Potential participants for the nested qualitative study who are not approached or who
15
16 442 decline will have no specific interventions / procedures.

17
18
19 443 *Withdrawal of Study Participants*

20
21 444 The nature of a cluster randomised study is such that it is not possible for the
22
23 445 participant to withdraw from the “cluster” unless she changes maternity unit part way
24
25 446 through her pregnancy. We plan to collect routinely recorded anonymised data;
26
27 447 patients have the right to opt out of having their data used – if this happens their data
28
29 448 would be excluded from the study database (e.g. under the Confidentiality and
30
31 449 Security advisory Group Report 2002 and the Data Protection Act (1998)
32
33 450 requirements for fair processing of data). Participants in the nested qualitative study
34
35 451 who wish to withdraw will be allowed to do so. Their data will be retained and used,
36
37 452 unless they additionally indicate that they wish to withdraw their data.

38
39
40 453 **RANDOMISATION**

41
42 454 *Randomisation Procedures*

43
44
45 455 This is a cluster-randomised, stepped-wedge design trial wherein maternity units
46
47 456 rather than individual patients are randomised. All units will implement the fetal
48
49 457 movement monitoring intervention at some point during the trial; the random element
50
51 458 is the time point at which this will occur, the so-called “step” of the stepped-wedge
52
53 459 design. Participating maternity units will be blinded to their randomly allocated time
54
55 460 point until the time this is required to be revealed to enable the necessary training in
56
57 461 the implementation of the intervention to be delivered. Primary and secondary
58
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2
3 462 outcomes of the trial will be gathered in a blinded manner via routinely collected data
4
5 463 sources.

6
7 464 Maternity units which are in close proximity to each other will be grouped for the
8
9 465 purposes of randomisation. This will assist with the feasibility of delivering the training
10
11 466 for and implementation of the intervention. Furthermore, this local synchronisation of
12
13 467 the intervention implementation will minimise the chances of contamination
14
15 468 (introduction of the intervention prematurely) from maternity units which have already
16
17 469 implemented the intervention to those not yet randomised.

18
19
20 470 The order in which the groups of maternity units step in to implement the intervention
21
22 471 will be determined by computer generated random numbers from a uniform
23
24 472 distribution. The randomisation list will be held by the Edinburgh Clinical Trials Unit
25
26 473 (ECTU). The identities of the research team staff whose roles in the trial require them
27
28 474 to be unblinded to randomisation codes will be recorded in the trial master file (TMF).

29
30
31 475 *Treatment Allocation*

32
33 476 Participating sites will be randomised to different schedules for implementing the
34
35 477 intervention. All units will be providing conventional treatment at baseline according
36
37 478 to local practice – this is the treatment established before the study starts. Sites will
38
39 479 be randomised to “active” treatment in turn as described above. Active treatment will
40
41 480 consist of a package of care consisting of a management plan for identification and
42
43 481 delivery of the ‘at risk’ fetus, together with strategies for increasing pregnant women’s
44
45 482 awareness of the need to report RFM early. The recommended management plan for
46
47 483 identification and delivery of the “at risk” fetus is shown in Figure 2. Practice change
48
49 484 in the active units will be achieved by: (i) written/email information to all clinicians
50
51 485 (doctors, midwives and ultrasonographers) in each unit about the study protocol and
52
53 486 amendment of the local protocol for Reduced Fetal Movements (RFM) to that of the
54
55 487 study protocol; (ii) a short web-based training package taking approximately one hour
56
57 488 to complete for all clinicians in each centre and (iii) training /information sessions to
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2
3 489 run in each unit and (iv) posters in each unit to describe the practice change.
4
5 490 Strategies for encouraging clinicians to increase pregnant women's awareness of
6
7 491 fetal movement will include all the above and also a fetal movement leaflet for
8
9 492 pregnant women (shown in Supplementary Information 1). The Norwegian quality
10
11 493 improvement study showed inconclusive results regarding the effect of the
12
13 494 intervention in non-European women.⁴⁰ To attempt to address this, the AFFIRM
14
15 495 information leaflet was available in 12 languages including: Arabic, Bengali, English,
16
17 496 Hindi, Hungarian, Latvian, Lithuanian, Mandarin, Polish, Russian and Urdu.
18
19 497 Furthermore, by including staff education which highlighted the need to ask women
20
21 498 about fetal movements in routine antenatal consultations as many women as
22
23 499 possible should have received information about what to do if they perceive RFM.

24
25
26 500 Once units have begun active treatment it is not anticipated that they will return to
27
28 501 conventional treatment. We will conduct an audit of women presenting with reduced
29
30 502 fetal movements and assess the proportion of staff completing the online training to
31
32 503 assess the extent to which sites have followed the intervention plan. Units will be
33
34 504 informed about treatment allocation as near as possible to the implementation of the
35
36 505 "active" treatment. For practical purposes, we anticipate that each unit will need
37
38 506 around three months' notice before the "active" treatment is introduced, hence units
39
40 507 will be informed of the timing of their treatment allocation (step) three months before
41
42 508 the active treatment is due to start. The treatment allocation will not be administered
43
44 509 blind and there are no restrictions on concomitant care or other interventions during
45
46 510 the study, hence there is no need for emergency unblinding and there are no
47
48 511 stopping rules for the study.

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51 512

52 53 513 **DATA COLLECTION**

54
55
56 514 For the main trial, data will be accessed from the information routinely collected
57
58 515 during the clinical management of the patient. For consistency, we will normally only
59
60

1
2
3 516 include data items which become available within four months after the delivery date
4
5 517 in question, although we may seek advice from the independently-chaired trial
6
7 518 steering committee (TSC) about exceptions as they arise. Different data sources will
8
9 519 be used for different regions of the study: (i) In Scotland the source data will be
10
11 520 SMR2 and the Scottish Birth record, (ii) In Ireland the source data will be the National
12
13 521 Perinatal Reporting System (NRPS http://www.esri.ie/health_information/nprs), (iii) In
14
15 522 Northern Ireland, the source data will be the Northern Ireland maternity Statistics
16
17 523 database (NIMATS), (iv) In England and Wales, the source data will be the ONS, or
18
19 524 other relevant body. Data will be collected retrospectively on an annual basis from all
20
21 525 sources. We will assume that data unavailable four months after the woman
22
23 526 delivered is likely to be unobtainable (but see note in Study Design section above).
24
25 527 Thus, data on the first year of the study will be collected at month 16; data on the
26
27 528 second year will be collected at month 28 etc.

29
30 529 Data are routinely collected. A formal request for data access will be made at the
31
32 530 start of the study. This will require (i) in Scotland – Privacy Advisory Committee
33
34 531 approval and a formal approach to NHS Scotland Information Services Division (ISD)
35
36 532 (ii) in Ireland a formal approach to NRPS (iii) NIMATS in Northern Ireland (iv) in
37
38 533 England and Wales a formal approach will be made to the relevant bodies.

39
40 534 Data will then be sent to the electronic Data Research and Innovation Service
41
42 535 (eDRIS) National Safe Haven (NHS National Services Scotland) by secure file
43
44 536 transfer protocol (or other similar) for storage and subsequent analysis within a
45
46 537 secure project area (dedicated to the AFFIRM study). Further information on the
47
48 538 National Safe Haven is available at [http://www.isdscotland.org/Products-and-](http://www.isdscotland.org/Products-and-Services/eDRIS/Becoming-an-eDRIS-User/#NSS-National-Safe-Haven)
49
50 539 [Services/eDRIS/Becoming-an-eDRIS-User/#NSS-National-Safe-Haven](http://www.isdscotland.org/Products-and-Services/eDRIS/Becoming-an-eDRIS-User/#NSS-National-Safe-Haven). Briefly, the
51
52 540 National Safe Haven is located on a secure server, in which trusted and authorised
53
54 541 researchers can analyse individual level data while maintaining the utmost
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1
2
3 542 confidentiality. It is anticipated that all study analysis will be done within the Safe
4
5 543 Haven, using one of the available statistical packages (e.g. R, SPSS).
6

7 544 Identifiers on Scottish data within the National Safe Haven are concealed from
8
9 545 researchers. Data from outwith Scotland will be anonymised before submission to the
10
11 546 National Safe Haven. We propose that data submitted to the National Safe Haven
12
13 547 will be “anonymised” by the data provider. However, we propose that the
14
15 548 anonymisation link will be retained at the source so that it will be possible to re-link
16
17 549 data retrospectively. The rationale for retaining the ability of local data guardians to
18
19 550 re-link data is because it is important to retain the possibility of identifying individual
20
21 551 patients retrospectively. Examples include: (i) It is possible that some additional
22
23 552 important data may be available at a late stage on individual participants – e.g. in the
24
25 553 scenario where the woman or baby had a major adverse event and spent a long time
26
27 554 in hospital before discharge or death and (ii) Although our protocol and outcome
28
29 555 analysis does not require identifiable data, we believe this will be a ‘once in a lifetime’
30
31 556 study, and that subsequent secondary analyses could yield important information for
32
33 557 patients and for policy makers. If retrospective identification is not possible, this will
34
35 558 limit further analysis. One likely example of future analyses is to determine the effect
36
37 559 of the intervention on different causes of stillbirth. This is outwith the scope of the
38
39 560 current protocol, but could be done relatively straightforwardly, by linking nationally
40
41 561 recorded information on “cause” of stillbirth to our study database. We anticipate that
42
43 562 such additional analyses would require additional ethics approval, but without a
44
45 563 process by which to re-link data, it will not be possible to perform such subsequent
46
47 564 analyses.
48

49
50 565 All Investigators and study site staff involved with this study will comply with the
51
52 566 requirements of the Data Protection Act 1998 (or equivalent for those outwith the UK)
53
54 567 with regard to the collection, storage, processing and disclosure of personal
55
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1
2
3 568 information and will uphold the Act's core principles. Published results will not contain
4
5 569 any personal data that could allow identification of an individual participant.
6

7
8 570 In addition to the data recorded above, all sites will be asked to provide a copy of
9
10 571 their guidelines around (i) maternal awareness of RFM and (ii) management of
11
12 572 women presenting with RFM. Copies of guidelines will be sought by the study office
13
14 573 (a) at the start of the study (b) immediately before initiation of the intervention in each
15
16 574 specific unit and (c) six months after initiation of the intervention in each specific unit.
17

18 575 For the nested qualitative study, we will perform interviews of healthcare workers and
19
20 576 a small nested cohort of pregnant women about their experiences of fetal movement
21
22 577 and of this intervention. We shall ensure a diversity of age and include nulliparous
23
24 578 and multiparous women (n=30 in total). Ten interviews will be conducted with each of
25
26 579 the following groups of health care providers: obstetricians, midwives and
27
28 580 sonographers/radiologists. The interviews will take a semi-structured format
29
30 581 (sensitising and piloting interviews will be conducted prior to the commencement of
31
32 582 the trial and in the first month of the nested qualitative study). This format will ensure
33
34 583 the same categories of data will be obtained from each participant but also allow
35
36 584 individual responses to be fully explored.
37
38

39 585

40 41 586 **STATISTICS AND DATA ANALYSIS**

42 43 44 587 *Sample size calculation*

45
46 588 The sample size is the number of women delivering in hospitals participating in the
47
48 589 study. This was initially planned to include sites in Scotland, totalling around 58,000
49
50 590 deliveries per year with 16 consultant led maternity units, 20 smaller units each
51
52 591 delivering less than 350 babies per year, and seven units delivering less than five
53
54 592 births per year. The units involved in Perinatal Ireland (an all-Ireland research
55
56 593 consortium across 7 academic sites in Ireland currently funded by the Health
57
58
59
60

1
2
3 594 Research Board, Ireland) have 50,000 births per year with seven large sites.
4
5 595 Combining one or two of the smaller units and one larger unit into a single “hospital
6
7 596 group” for each local area could provide 24 hospital “groups” – the details of hospital
8
9 597 groupings will be reviewed and finalised immediately prior to randomisation. In total,
10
11 598 36 sites expressed interest in participating in the study, although 2 were unable to
12
13 599 participate in the study and withdrew before randomisation. In total, 34 units were
14
15 600 randomised, these were situated throughout the UK and Ireland (10 in England, 4 in
16
17 601 Ireland, 15 in Scotland and 5 in Wales) with 143,140 births per annum.

18
19
20 602 We calculated statistical power using the methodology for stepped wedge designs
21
22 603 proposed in Hussey and Hughes (2007).⁴¹ First, we analysed stillbirth event data
23
24 604 from the Scottish Perinatal and Infant Mortality and Morbidity Report (SPIMMR)
25
26 605 covering years 2005-2010 ¹⁶ to determine estimates of between- and within-unit
27
28 606 variability in stillbirth rate. Analysis was by generalized linear mixed model for binary
29
30 607 outcomes. The power calculation, as per equations (#7) and (#8) in ⁴¹ assumed:
31
32 608 significance level 5%; analysis by generalized linear mixed model; deliveries equally
33
34 609 distributed across hospital groupings; baseline stillbirth rate 0.438% ¹⁶; cluster
35
36 610 coefficient of variation 0.333.

37
38
39 611 Finally, the statistical power depends on the number of groups in which the
40
41 612 intervention is implemented at each stage of the stepped wedge design and the
42
43 613 duration of recruitment at each “step”. Our study design proposes sequential
44
45 614 introduction of the intervention into three hospital groups at a time in eight steps at
46
47 615 four month intervals. This would give 92.4% power to detect a 30% risk reduction
48
49 616 under the intervention and 80.7% power to detect a 25% reduction. A 30% risk
50
51 617 reduction was seen in the Norwegian study; the anticipated effect sizes of 25% and
52
53 618 30% relative reduction take into account that the intervention will not have the power
54
55 619 to reduce all stillbirths, since 20% of stillbirths in Ireland ⁴² and 15% in Scotland ¹⁶ are
56
57 620 associated with congenital anomaly.

1
2
3 621 The power actually achieved in the study will be slightly lower, as deliveries during
4
5 622 the two month “transition” period following implementation of the intervention in a site
6
7 623 will not be included in the analysis. The effect of this was explored using the Stata
8
9 624 function steppedwedge,⁴³ which showed the statistical power would become 88.2%
10
11 625 (30% risk reduction) and 74.6% (25% risk reduction). It is anticipated that
12
13 626 unavailability of data and women asking to withdraw their data will be less than 1%.

14
15
16 627 *Proposed analyses*

17
18 628 For the binary primary and secondary outcomes, data will be analysed by
19
20 629 generalized linear mixed model with a random effect for hospital and fixed effects for
21
22 630 the intervention implementation and study time period. A site by intervention
23
24 631 interaction random effect will be included in the model and retained if it explains an
25
26 632 important proportion of the variability in outcomes. The primary analysis of data will
27
28 633 be on an intention to treat basis (the design of the trial means it is not possible to
29
30 634 determine individual patient /caregiver compliance with the intervention). An “on
31
32 635 treatment” variable will be calculated for which women will be grouped as active or
33
34 636 control according to when the intervention was actually implemented in their site,
35
36 637 instead of when the site was randomised to implement the intervention. The primary
37
38 638 outcome will be reanalysed in two sensitivity analyses. Firstly, we will perform the
39
40 639 analysis according to the actual timing of the implementation of the intervention
41
42 640 rather than the randomised timing of the intervention using the “on treatment”
43
44 641 classification. Secondly, we will perform the analysis in the subgroup of sites who
45
46 642 were deemed to have implemented the intervention effectively according to the
47
48 643 perception of the Principal Investigator at each site. The accuracy of this perception
49
50 644 will be confirmed with the findings of a site audit (details in Appendix 3). There will be
51
52 645 no attempt to correlate the impact of the intervention according to the results of the
53
54 646 site audit.
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1
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3 647 There are no planned imputations for missing data. However, if the missing data rate
4
5 648 for smoking status during pregnancy is relatively high an imputation technique will be
6
7 649 devised. The imputation method will be informed using smoking history at booking
8
9 650 and age at delivery ⁴⁴. A pre-specified subgroup analysis will be performed for babies
10
11 651 with and without congenital anomalies, and will be implemented by testing for an
12
13 652 intervention by congenital anomaly interaction added to the generalised linear mixed
14
15 653 model described above. No formal interim analyses for efficacy or safety will be
16
17 654 performed. A full statistical analysis plan will be finalised prior to locking of the study
18
19 655 database.

21 656 *Qualitative Data*

22
23
24 657 For the nested qualitative study, the data will be audio recorded and transcribed.
25
26 658 The data will be coded thematically and an analytical framework developed to make
27
28 659 sense of patient experience of fetal movement and the intervention and also health
29
30 660 care providers' perspectives and experiences. NVivo will be utilised to support the
31
32 661 analysis.

34 662 *Process outcomes*

35
36
37 663 The process outcomes being assessed by the (rates of induction of labour, number
38
39 664 of women presenting with reduced fetal movements, interval between perceiving fetal
40
41 665 movements and presenting to hospital) will be analysed using the same methods as
42
43 666 for the main trial, with the exception of the continuous outcome (interval between
44
45 667 perceiving fetal movements and presenting to hospital) which will be analysed using
46
47 668 a normal linear mixed model.

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52 670 **ADVERSE EVENTS**

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54
55 671 This is not a Clinical Trial of an Investigational Medicinal Product (CTIMP) so adverse
56
57 672 events will not be formally reported. Stillbirth and other measures of fetal and
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2
3 673 maternal morbidity are outcomes of the study. The purpose of the intervention is to
4
5 674 reduce such adverse events. Therefore, due to the low risks for this trial, a separate
6
7 675 DMC is not required and the Trial Steering Committee (TSC) will cover any
8
9 676 responsibilities normally allocated to a DMC. If considered necessary, the TSC may
10
11 677 review unblinded data for the study, including morbidity and mortality indices. No
12
13 678 other adverse event reporting will be undertaken.

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17 680 **TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS**

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19
20 681 The trial will be coordinated by a Project Management Group, consisting of the grant
21
22 682 holders and the Trial Manager. The Chief Investigator (JN) will lead the project
23
24 683 management group. The Trial Manager will oversee the study and will be
25
26 684 accountable to the Chief Investigator. A TSC will be established to oversee the
27
28 685 conduct and progress of the trial. The terms of reference and a draft template for
29
30 686 reporting will be ratified in one of the early meetings of the TSC.

31
32
33 687 Investigators and institutions involved in the study will permit trial related monitoring
34
35 688 and audits on behalf of the co-sponsors (ACCORD: Academic and Clinical Central
36
37 689 Office for Research & Development - Joint office for University of Edinburgh and
38
39 690 NHS Lothian, Sponsor contact: ray.french@ed.ac.uk), research ethics committee
40
41 691 (REC) review, and regulatory inspection(s). In the event of an audit or monitoring, the
42
43 692 Investigator agrees to allow the representatives of the sponsor direct access to all
44
45 693 study records and source documentation. In the event of regulatory inspection, the
46
47 694 Investigator agrees to allow inspectors direct access to all study records and source
48
49 695 documentation.

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3 698 *Study monitoring and audit*
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5 699 The sponsor determined that as no individual participants were recruited to the
6
7 700 intervention, and it was not a clinical trial of an investigational medicinal product
8
9 701 (CTIMP) no formal monitoring and audit was required.
10

11 702

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13
14 703 *Good Clinical Practice and Ethical Conduct*
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16
17 704 The study will be conducted in accordance with the principles of the research
18
19 705 governance framework operational and good clinical practice in the relevant country.
20

21 706 A favorable ethical opinion has been obtained from the Scotland A REC (Reference
22
23 707 13/SS/0001) and local research and development approval has been obtained prior
24
25 708 to commencement of the study.
26

27
28 709 Local study investigator(s) will be appointed to each site (or for small units, groups of
29
30 710 sites). S/he will be responsible for the overall conduct of the study at the site and
31
32 711 compliance with the protocol and any protocol amendments.
33

34 712

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36
37 713 **STUDY CONDUCT RESPONSIBILITIES**
38

39 714 *Protocol amendments*
40

41
42 715 Any changes in research activity, except those necessary to remove an apparent,
43
44 716 immediate hazard to the participant in the case of an urgent safety measure, will be
45
46 717 reviewed and approved by the Chief Investigator and Sponsor. Amendments to the
47
48 718 protocol will be submitted in writing to the appropriate REC and local Research and
49
50 719 Development (R&D) department for approval prior to participants being enrolled into
51
52 720 an amended protocol.
53

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3 722 *Protocol violations and deviations*
4

5 723 Investigators will not implement any deviation from the protocol without agreement
6
7 724 from the Chief Investigator and appropriate REC and R&D department approval
8
9 725 except where necessary to eliminate an immediate hazard to trial participants. In the
10
11 726 event that an Investigator needs to deviate from the protocol, the nature of and
12
13 727 reasons for the deviation will be recorded. If this necessitates a subsequent protocol
14
15 728 amendment, this will be submitted to the REC, and local R&D department for review
16
17 729 and approval if appropriate.
18
19

20 730 *Serious breach requirements*
21

22
23 731 A serious breach is one which is likely to effect to a significant degree (a) the safety
24
25 732 or physical or mental integrity of the participants of the trial; or b) the scientific value
26
27 733 of the trial. If a potential serious breach is identified by the Chief investigator,
28
29 734 Principal Investigator or delegates, the co-sponsors
30
31 735 (accord.seriousbreach@ed.ac.uk) will be notified within 24 hours. It will be the
32
33 736 responsibility of the co-sponsors to assess the impact of the breach on the scientific
34
35 737 value of the trial, to determine whether the incident constitutes a serious breach and,
36
37 738 if so, report it to the REC.
38

39 739 All violations will be assessed by the sponsor(s) to ascertain if they meet the criteria
40
41 740 for a serious breach. If the sponsor(s) deem the incident to be a violation that does
42
43 741 not constitute a serious breach from the protocol when identified, corrective and
44
45 742 preventative actions will be taken where appropriate and they will be recorded in file
46
47 743 notes, held within the TMF and ISF.
48

49
50 744 *Study record retention*
51

52
53 745 All study documentation will be kept for a minimum of 5 years from the protocol
54
55 746 defined end of study point. When the minimum retention period has elapsed, study
56
57 747 documentation will not be destroyed without permission from the sponsor.
58
59
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5 749 *End of study*

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7
8 750 The end of study date was finalised in the protocol after the study commenced; the
9
10 751 agreed end of study date is 31/12/2016. The Investigators and/or the trial steering
11
12 752 committee and/or the co-sponsor(s) have the right at any time to terminate the study
13
14 753 for clinical or administrative reasons.

15
16 754 The end of the study will be reported to the REC within 90 days, or 15 days if the
17
18 755 study is terminated prematurely. The Investigators will inform participants of the
19
20 756 premature study closure and ensure that the appropriate follow up is arranged for all
21
22 757 participants involved. A summary report of the study will be provided to the REC and
23
24 758 Regulatory Authority within 1 year of the end of the study.

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30 760 **REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS**

31
32 761 Ownership of the data arising from this study resides with the study team. On
33
34 762 completion of the study, the study data will be analysed and tabulated, and a clinical
35
36 763 study report will be prepared in accordance with good clinical practice guidelines.
37
38 764 The clinical study report will be used as the basis for publication and presentation at
39
40 765 scientific meetings. Investigators have the right to publish orally or in writing the
41
42 766 results of the study. Summaries of results will also be made available to Investigators
43
44 767 for dissemination within their clinics (where appropriate and according to their
45
46 768 discretion).

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51 770 **DISCUSSION**

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54 771 The data provided by this study will inform the information given to women about
55
56 772 reduced fetal movements and their management when they present to maternity
57
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1
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3 773 services; which has been recurrently identified by Confidential Enquiries into
4
5 774 antepartum stillbirths as suboptimal^{26 27}. Data from the AFFIRM study will be able to
6
7 775 be compared to results from two other active studies which aim to improve mothers
8
9 776 awareness and reporting of reduced fetal movements. My Babies Movement
10
11 777 (ACTRN 12614000291684) is stepped-wedge cluster trial of a mobile phone
12
13 778 application to help women get to know their baby's movements, to be mindful of
14
15 779 movements every day and not to wait to report concerns to their maternity care
16
17 780 provider. The Mindfetalness study (NCT02865759) is a cluster trial of 39,000 women
18
19 781 randomised to routine antenatal care or the Mindfetalness brochure and website.⁴⁵
20
21 782 Women participating in the Mindfetalness process will spend 15 minutes each day
22
23 783 getting to know their babies movements and will specifically be encouraged to
24
25 784 contact their health provider if their perceive reduced fetal movements. This primary
26
27 785 outcome of this study is an Apgar score <7 at 5 minutes; stillbirth and perinatal
28
29 786 deaths will be recorded as tertiary endpoints of this study.⁴⁵ These large studies will
30
31 787 provide much needed robust evidence to determine whether increased maternal
32
33 788 awareness of reduced fetal movements combined with a standardised management
34
35 789 protocol to identify acute or chronic fetal compromise can reduce stillbirth³².

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791 **PEER REVIEW**

792 This project has been peer reviewed internally, and was externally peer reviewed
793 during the process of securing funding from the Chief Scientist's Office of the
794 Scottish Government, Tommy's and Sands.

795

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1
2
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4
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6
7 802 independent research funded by the National Institute for Health Research (NIHR).
8
9 803 The views expressed are those of the author(s) and not necessarily those of the
10
11 804 NHS, the NIHR or the Department of Health.
12

13 805

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16
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18
19 808 Higgins (University College Dublin, National Maternity Hospital, Dublin).
20

21 809

22 23 810 **CONTRIBUTIONS**

24
25 811 Contributors AEPH, CJW, SJES, CJC, SCB, MRD, SW and JEN were involved in
26
27 812 developing the trial design. AEPH, CJW, SJES, AR and JEN were involved in
28
29 813 drafting and revision of the article. CJW and AR were involved in drafting the
30
31 814 statistical aspects of the protocol. JS provided feedback on behalf of a stakeholder
32
33 815 organisation. AEPH, CJW, SJES, CJC, SCB, JFF, MG, AH, FMM, EM, AR, MRD, JS,
34
35 816 SW and JEN were involved in preparing the overall study design. AEPH, JEN and
36
37 817 MRD prepared education videos for online training. AEPH, SJES, SJS, MG, AH,
38
39 818 FMM and JEN facilitated recruitment of sites. AEPH, CJW, SJES, CJC, SCB, JFF,
40
41 819 MG, AH, FMM, EM, AR, MRD, JS, SW and JEN will be involved in the collection,
42
43 820 management, analysis and interpretation of data and final writing of the trial report.
44

45 821

46 47 822 **COMPETING INTERESTS**

48
49 823 None declared.
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824 **ABBREVIATIONS**

825 ACCORD Academic and Clinical Central Office for Research & Development -
826 Joint office for University of Edinburgh and NHS Lothian

827 BMI Body Mass Index

828 CTG Cardiotocograph

829 CTIMP Clinical Trial of an Investigational Medicinal Product

830 ECTU Edinburgh Clinical Trials Unit

831 FGR Fetal growth restriction

832 MHRA Medicines and Healthcare products Regulatory Agency

833 NICE National Institute for Health and Social Care Excellence

834 NIHR National Institute for Health Research

835 NIMATS Northern Ireland Maternity Statistics database

836 NRPS National Perinatal Reporting System

837 ONS Office of National Statistics

838 PSANZ Perinatal Society of Australia and New Zealand

839 RCOG Royal College of Obstetricians and Gynaecologists

840 R&D Research and Development

841 REC Research Ethics Committee

842 RFM Reduced Fetal Movements

843 SPIMMR Scottish Perinatal and Infant Mortality and Morbidity Report

844 TMF Trial Master File

845 TSC Trial Steering Committee

846 WHO World Health Organisation

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3 996 **FIGURE LEGENDS**
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5 997 Figure 1 - Stepped wedge design. The shaded areas (both light and dark) indicate
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7 998 periods in which the interventions are being implemented. The lighter areas indicate
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9 999 the “transition” period during which data will not be collected for the control or
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11 1000 intervention group. The order in which hospital groupings implement the interventions
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13 1001 will be determined via randomization.
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15
16 1002 Figure 2 – Flow chart for the management of women presenting with reduced fetal
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18 1003 movements for sites implementing the AFFIRM study. Abbreviations: AC - abdominal
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20 1004 circumference, CTG- cardiotocograph, DVP - deepest vertical pool, EFW - estimated
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22 1005 fetal weight, FGR - fetal growth restriction, LV - liquor volume, RFM - reduced fetal
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24 1006 movement, USS - ultrasound scan.
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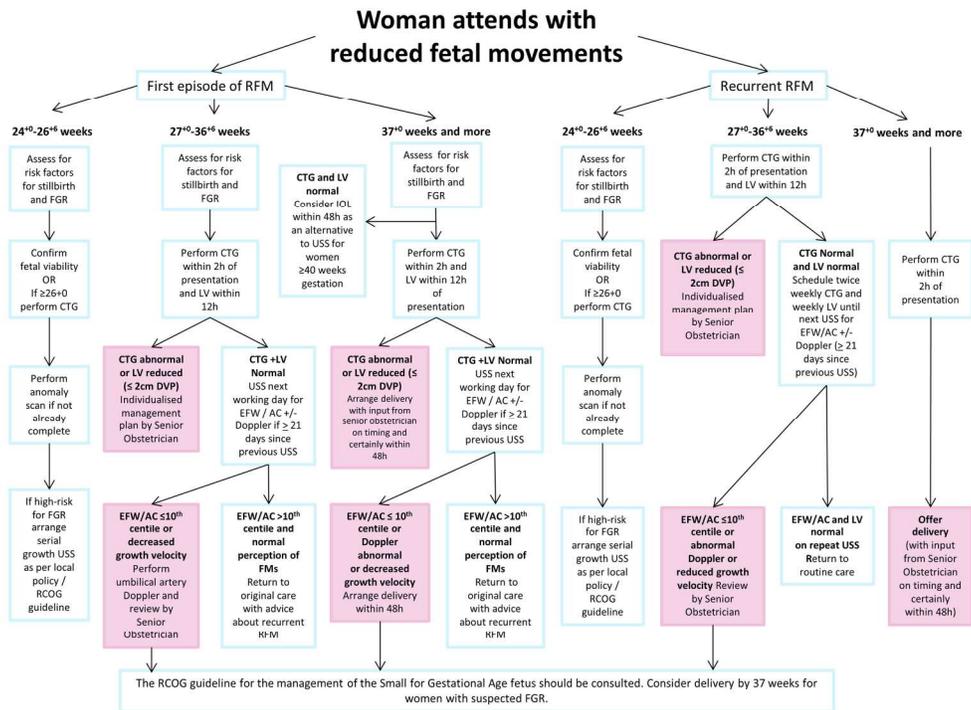
Hospital groupings	Months since Start of Trial								
	1-4	5-8	9-12	13-16	17-20	21-24	25-28	29-32	33-36
1-3		Light	Dark						
4-6			Light	Dark	Dark	Dark	Dark	Dark	Dark
7-9				Light	Dark	Dark	Dark	Dark	Dark
10-12					Light	Dark	Dark	Dark	Dark
13-15						Light	Dark	Dark	Dark
16-18							Light	Dark	Dark
19-21								Light	Dark
22-24									Light

Stepped wedge design. The shaded areas (both light and dark) indicate periods in which the interventions are being implemented. The lighter areas indicate the "transition" period during which data will not be collected for the control or intervention group. The order in which hospital groupings implement the interventions will be determined via randomization.

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Flow chart for the management of women presenting with reduced fetal movements for sites implementing the AFFIRM study. Abbreviations: AC - abdominal circumference, CTG- cardiotocograph, DVP - deepest vertical pool, EFW - estimated fetal weight, FGR - fetal growth restriction, LV - liquor volume, RFM - reduced fetal movement, USS - ultrasound scan.

190x142mm (300 x 300 DPI)

WHO TO CONTACT IF YOU ARE CONCERNED: (space for sticky with local contact information)



APS Group Scotland
DPPAS33137
Version 3 March 2015



In touch with **YOUR BABY**

A guide to your baby's
movements during
pregnancy



For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

Why are my baby's movements important?

Why are we asking women to get to know their baby's movements?

One of the easiest ways to tell if your baby is healthy is to be aware of how much he or she is moving. Every baby is different and we are asking women to take time to become familiar with their baby's own individual pattern of movements. A reduction or change in **your** baby's movements is what is important.

What can affect my baby's movements?

You are less likely to be aware of your baby's movements when active or busy. Some drugs e.g. strong pain relief or sedatives can get into an unborn baby's circulation and affect the movements. Alcohol and smoking (active and passive smoking) may also affect the baby.

Why are my baby's movements important?

If you notice your baby is moving less than usual, or the pattern of movements has changed, this could be the first sign that your baby may not be well or is not growing properly in the womb. Research has shown that a reduction in the baby's movements may indicate an increased risk of stillbirth. You may hear your midwife or doctor referring to 'reduced fetal movement', or RFM for short.

What are the risks of stillbirth?

Stillbirth affects one in 200 babies after 24 weeks gestation and is one of the most common of the serious complications of pregnancy, affecting the lives of around 4,000 families every year in the UK.

One of the easiest ways to tell if your baby is healthy is to see how much he or she is moving. This booklet tells you what to look out for during your pregnancy.



Every baby is different. It is good to get to know your baby's own movements and the pattern of their sleeping and waking and report to us if you notice a reduction in these movements.

Try to get to know the times of the day when you are most likely to feel your baby move.



18-24 WEEKS



24-36 WEEKS



Most women begin to feel their baby move between 18-24 weeks. At first it may feel like 'bubbles', 'flutterings' or 'like trapped wind'. These are often very short and stop and start. It might take you a little while to be sure what you are feeling. But you will soon get to know the feelings. If this is your second baby, you will know what to look out for and may recognise your baby moving sooner.

Everyone is different when it comes to their movements. There are many reasons you might not feel movements as early as you expect. This includes your body weight, the position of your baby and the location of your placenta. What is important is your baby is growing well. Your midwife will be able to discuss this with you further at your 22 week check.

You will have your own way of describing your baby's own movements. Women often describe their baby's movements as 'rolling', 'kicking', 'pushing', 'jabs', 'elbowing' and 'stretches'.

Between 24-36 weeks you will start to recognise your baby's movements more quickly and become more used to the feeling. It is usually easier to feel your baby's movements when you are lying down, e.g. at night time. It is harder to feel your baby move when you are on your feet and moving around.

Try to get to know the times of the day you are most likely to feel your baby move. This will help you to know if he or she is moving less than normal or if movements have stopped.

Occasionally your baby will get hiccups. These do not count as movements. If you are unsure what you should expect when your baby hiccups, speak to your midwife.



Appendix 2 - Audit of compliance with AFFIRM protocol

Compliance with the AFFIRM management protocol (the management plan for women presenting with reduced fetal movement) will be determined by to means:

A) Telephone / email contact with Principal Investigators at each site to determine which aspects of the AFFIRM protocol have been implemented effectively.

This will involve email contact with Principal Investigators to alert them to the request for information, an email detailing the information required, and then a phone call to elicit the information (unless it had already been supplied). Investigators will be asked which of the following elements they had implemented: issuing leaflets to all pregnant women, cardiotocography within 2 hours of presentation, measurement of amniotic fluid volume within 12 hours of presentation, growth scan by the next working day for all women presenting with reduced fetal movement (and who had not had a growth scan within the last three weeks, or who were not being induced within 48 hours), and induction of labour within 48 hours for women presenting with recurrent reduced fetal movement at or after 37 weeks gestation. "Effective implementation" was defined as the above management for 4/5 of these elements for 80% or more of the time.

B) An audit to determine whether the perception of the site Principal Investigator is supported by review of actual decision making will be performed for the following elements: cardiotocography within 2 hours of presentation, measurement of amniotic fluid volume within 12 hours of presentation, growth scan by the next working day for all women presenting with reduced fetal movement (and who had not had a growth scan within the last three weeks, or who were not being induced within 48 hours), and induction of labour within 48 hours for women presenting with recurrent reduced fetal movement at or after 37 weeks gestation.

This will be conducted by asking sites to complete an audit of the management of all women presenting with reduced fetal movement over the course of one calendar month. Sites will be asked to complete an audit form for each participant. The audit form template (see below) has been generated by the central

1 AFFIRM study team; anonymized forms will be analysed centrally. There will not be an attempt to corroborate Principal Investigator perception of the
2
3 proportion of women who were given leaflets, nor will there be any attempt to incorporate the proportion of staff who had completed the e-learning
4
5 package into analysis of whether any specific site has implemented the intervention or not.
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For peer review only

Compliance with AFFIRM reduced fetal movements protocol, One month data collection AUDIT [Month & Year] Unit name: [Name of Hospital]

If you assess a woman with reduced fetal movements (RFM), please complete the questions below. Do not worry if the woman has been seen in other areas of the hospital by other staff, we would rather have multiple reports for the same woman than miss episodes of RFM.

INSERT Patient Sticker (or WRITE name and CHI /NHS number)				AREA WHERE SEEN (CIRCLE) Triage / Labour ward / Day Assessment Unit (DAU) Other (specify area i.e. antenatal ward): _____						
Date and time of presentation with reduced fetal movements.	DATE: ____/____/____ TIME ____:____ am / pm			GESTATION AND EDD:	____ WEEKS ____ DAYS EDD: _____					
Referred by (TICK BOX):	Self	Community Midwife	GP	ANC	Triage	DAU	Other (specify: _____)			
What was the primary reason for attending/phoning? (TICK BOX):	Reduced Fetal Movements			Other (specify: _____)						
How many times has the woman attended before this visit, with RFM? (TICK BOX):	None – first attendance		Once previously	Unknown	Multiple times (please provide the gestation at each presentation i.e. 30+6)	1	2	3	4	5
What was the time interval from the woman first being aware of reduced fetal movements and attending the hospital (in hours)?					HOURS: _____					
Has she been given a leaflet "Your baby's movements in pregnancy"? (TICK BOX):	Yes – she already has one		Yes – I have given one to her today		Locally Created Leaflet Given			NO		
Has this woman had a growth USS in this pregnancy? (TICK BOX):	No, she has not had a growth scan		Yes, within the last 3 weeks (date of scan): DATE: ____/____/____		Yes, but more than 3 weeks ago (date of scan): DATE: ____/____/____					

CONTINUATION: NHS/ CHI NUMBER:

Are any of the following risk factors for Fetal growth restriction present (CIRCLE all that apply)?							
Age ≥40 or ≤16	Smoker ≥20cpd	Known or suspected growth restriction	Congenital anomaly	Raised BP (essential hypertension, pre-eclampsia or pregnancy induced hypertension)	Previous pre-eclampsia	Diabetes or gestational diabetes	Previous FGR or stillbirth
What investigations were conducted during this episode of reduced fetal movement?							
Please record below the date and time that these investigations were completed or indicate if not performed.					Please provide the results (CIRCLE):		
CTG	Not performed	<input type="checkbox"/>	DATE: ___/___/___	TIME: ___:___ am/pm	Normal / Suspicious / Pathological		
Computerised CTG: YES / NO (CIRCLE)							
Liquor volume assessment on scan	Not performed	<input type="checkbox"/>	DATE: ___/___/___	TIME: ___:___ am/pm	Normal / Reduced / Increased		
Growth scan	Not performed	<input type="checkbox"/>	DATE: ___/___/___	TIME: ___:___ am/pm	Normal / EFW < 10 th centile/ AC < 10 th centile / EFW and AC < 10 th centile		
Umbilical Artery Doppler	Not performed	<input type="checkbox"/>	DATE: ___/___/___	TIME: ___:___ am/pm	Normal/.> 95 th centile/absent EDF/reversed EDF		
MCA Doppler	Not performed	<input type="checkbox"/>	DATE: ___/___/___	TIME: ___:___ am/pm	Normal/<5 th centile		
DELIVERY METHOD (If available)							
Was the woman offered induction of labour	YES / NO (CIRCLE) IF Yes, please provide date, time and method of the induction:			DATE: ___/___/___ TIME: ___:___ am/pm			
Was the woman offered elective caesarean section as a result of the reduced fetal movement?	YES / NO (CIRCLE) IF Yes, please provide date, time and reason:			DATE: ___/___/___ TIME: ___:___ am/pm		Please provide the reason for the elective Caesarean section:	



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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___ Page 1 ___
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___ Page 4 ___
	2b	All items from the World Health Organization Trial Registration Data Set	_Included throughout protocol_
Protocol version	3	Date and version identifier	___ Page 4 ___
Funding	4	Sources and types of financial, material, and other support	___ Pages 31-32 ___
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_Names and affiliations Page 1 and 2; Contributions Page 32_
	5b	Name and contact information for the trial sponsor	___ Page 27 ___
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_Not applicable_

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3		5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
4			___Page 27___
5			
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7			
8	Introduction		
9			
10	Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
11			__Pages 5-12__
12		6b	Explanation for choice of comparators
13			__Pages 8-10__
14	Objectives	7	Specific objectives or hypotheses
15			__Page 12__
16	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
17			__Pages 15-16 and Figure 1__
18			
19			
20	Methods: Participants, interventions, and outcomes		
21			
22	Study setting	9	Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
23			__Pages 15 & 24__
24			
25	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
26			__Pages 16-17__
27			
28	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
29			__Pages 19-20 and Figure 2__
30		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
31			__Not applicable in AFFIRM trial__
32		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
33			__Pages 19-20__
34		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
35			__Not applicable__
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3	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	__Pages 13-14__
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8	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	__Randomisation by site explained in Figure 1 and Pages 18-19__
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14	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	__Pages 23-25__
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17	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	__Page 23__
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20	Methods: Assignment of interventions (for controlled trials)			
21	Allocation:			
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23	Sequence generation	16a	Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	__Pages 18-19__
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29	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	__Page 19__
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33	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	__Page 19__
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36	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	__Page 19__
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39		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_ Not applicable in AFFIRM study__
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Methods: Data collection, management, and analysis

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5	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	__Pages 20-23__
6	methods			
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11		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	__Not applicable__
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14	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	__Pages 21-22__
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18	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	__Pages 25-26__
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21		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	__Pages 25-26__
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23		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	__Pages 25-26__
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27	Methods: Monitoring			
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29	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_DMC not required, explanation Pg 27__
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34		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	__Pages 20, 28-29__
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37	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	__Pages 26-27__
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40	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	__Page 15__
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Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	__Page 28__
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	__Page 28__
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	__Page 28__
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	__Not applicable__
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	__Pages 21-22__
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	__Page 32__
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	__Page 30__
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	__Page 27__
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	__Page 30__
	31b	Authorship eligibility guidelines and any intended use of professional writers	__Page 31__
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	__Not applicable__

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_Not Applicable__
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_Not Applicable__

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.